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THE ACTION OF CERTAIN DRUGS ON RESPIRATION*

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The close affinity between physiology and pharmacology means that progress in one of these spheres often leads to advance in the other. In what follows an attempt is made to illustrate such interrelations in a special field and to show how the growth of our knowledge of the regulation of respiration during the past 25 years has enabled us to analyse more closely the action of different drugs on respiration. I hope I will be pardoned if I dwell mainly on studies in which I have myself been engaged.

Some New Facts

It may be useful first to recall some of the new physiological facts. The demonstration by Hering (1927) and others of the important role of the carotid sinus for the regulation of the arterial blood pressure raised the question whether the sinus is also in some way concerned with the regulation of respiration. Mainly thanks to Heymans and his collaborators (1930) it soon became evident that an increased pressure in the sinus may provoke inhibition and that a lowering of the pressure may stimulate respiration so long as the sinus nerves are intact, whereas denervation of the sinuses eliminates the effects. By this time it was known that a tonic influence is exercised from the sinus region on the blood pressure and the heart rate, this being proved by the rise in pressure and increase in heart rate after section of the sinus nerves. It seemed quite natural to assume that the effect of the pressure on respiration was analogous. A certain confirmation appeared to be afforded by observations that section of the depressor nerves, together with denervation of both sinuses, produced increased respiration.

The discovery made by J. F. and C. Heymans (1927) that asphyxial blood stimulates peripheral end-organs of the depressor nerves and thereby causes an increased activity of the respiratory centre, and that, similarly, acapnic blood induces diminution or suspension of breathing, made it highly desirable to investigate whether the carotid sinus could also be influenced by the chemical composition of the blood. The well-known experiments carried out by Heymans, Bouckaert, and Dautrebande (1930) proved this to be the case. They showed convincingly that oxygen want stimulates respiration almost exclusively by way of a reflex elicited in the sinus and to a less extent the aortic regions. After their denervation the inhalation of a gas mixture poor in oxygen causes a depression of respiration. Carbon dioxide, on the other hand, acts directly on the centre as well as reflexly. Cyanides, lobeline, nicotine, and acetylcholine were also found to stimulate respiration by way of reflex. Thanks to further investigations by Bouckaert, Dautrebande, and Heymans (1931) it was possible to localize the chemical stimulation of the sinus region to the small carotid body. An analogous mechanism was demonstrated in the aorta by Comroe and Schmidt (1938).

The new results were at first received with a certain scepticism, as is shown by the following quotation from Haldane and Priestley (1935): "On the whole it seems that the reflex control of the breathing by chemical stimulation of the carotid nerve endings has not been established, at any rate as regards carbon dioxide. In respect of oxygen it has perhaps hardly been proved that the hyperpnoea is a carotid reflex apart from changes in circulation." There is in fact very little reason to connect the hyperpnoea during oxygen want with changes in circulation. Thus in the dog the arterial blood pressure remained constant when the animal breathed 5.2% oxygen, but respiration increased considerably (Euler and Liljestrand, 1936). After denervation of both sinuses the same gas mixture caused an elevation of the blood pressure, whereas respiration decreased and soon ceased. In the cat 8.25% oxygen led to a small rise in blood pressure and increased respiration. After denervation the effect of 8.25% oxygen was a rapid fall of the blood pressure and a decrease in respiration.

This new development made it doubtful whether the pressoreceptors have anything to do with the regulation of respiration. Euler and I (1937b) studied this question by perfusing both sinus regions by means of a Dale–Schuster pump. We found that an increase in the perfusion pressure often led to a reduction of ventilation, especially if the preceding pressure which had led to a stimulation of the chemoreceptors and overventilation was low. In other instances an increase in respiration resulted from high perfusion pressure, probably because sensory nerves within the sinus region were stimulated. No definite evidence was obtained of a direct inhibitory influence on breathing by the arterial blood pressure in the sinus region itself. Neither could we confirm the observation that denervation of the sinuses was followed by increased respiration. On the

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contrary, this operation regularly led to an increase in the alveolar carbon dioxide tension, which rose still more if the vagi were severed afterwards (Euler and Liljestrand, 1936). The effect was reduced, but not abolished, if the animals were breathing pure oxygen (Euler and Liljestrand, 1940). Part of the effect therefore must be due to oxygen want.

From these results it appeared that the chemoreceptors play a part in the regulation of respiration in normal anaesthetized animals. This was also clearly established by experiments by Euler, Liljestrand, and Zotterman (1939a) on the action potentials of the sinus nerve. These are of two kinds—great spikes, mainly appearing in bursts of impulses at each systole and elicited from the pressoreceptors, and much smaller potentials discharged continuously and partly due to chemical stimulation. It is possible to cut the branches of the sinus nerve from the sinus wall and thus to obtain the potentials from the chemical fibres practically isolated. The relation between the rate of impulses and the oxygen pressure in the inspired air was studied. Starting with 29% of oxygen in nitrogen, we found an increase of the impulse frequency already during air-breathing, indicating that the chemoreceptors begin to react at a rather high oxygen saturation of the haemoglobin. As the oxygen content of the inspired gas mixture went down, the number of potentials rose rapidly. Carbon dioxide elicited a corresponding effect already at an alveolar tension about 30 mm. Hg. It is interesting that De Castro, observing the carotid body under a low-power binocular microscope, found a great diminution of the organ during hyperpnoea due to carbon dioxide inhalation; during oxygen-breathing, however, the carotid body became somewhat larger than its normal size.

We confirmed the finding of Samaan and Stella (1935) that infusion of a cyanide solution was accompanied by a greatly increased number of small potentials in the sinus nerve, and we observed the same phenomenon after intravenous injection of lobeline or nicotine, which, as already mentioned, according to the Heymans school, exercise their action on respiration, mainly via the chemoreceptors. A typical difference, however, could be demonstrated between oxygen want or carbon dioxide accumulation and the alkaloids mentioned. Starting from the assumption that oxygen want and increased carbon dioxide tension stimulate the chemoreceptors by some common mechanism, presumably a change in the reaction within the cell to the acid side, we tried to influence it in the opposite direction by intravenous injection of moderate doses of ammonia. Even 0.5–2 ml. of a 0.5/N solution caused a complete temporary disappearance of the chemoreceptive impulses elicited by anoxaemia or by hypercapnia.

The same thing was found in respect of the action potentials during the infusion of cyanide. In this case pure oxygen could also counteract the cyanide, which supports the view that cyanides interfere with oxidation processes. The action potentials elicited by lobeline or nicotine, on the other hand, were not abolished by moderate doses of ammonia. We therefore concluded that these drugs act centrally to the point of stimulation involved in oxygen lack or carbon dioxide. This, in conjunction with the fact that a similar stimulating effect on the glomus is obtained also with other synaptotropic substances, such as acetylcholine, curarine, and potassium ions, and that they all paralyse the chemoreceptors in considerable concentrations, led us to consider whether they could act on the carotid body in a way analogous to their action on sympathetic ganglia. I will return to this question later on.

Effect of Cyanides

The effects of cyanides have been studied in some detail (Euler and Liljestrand, 1937a). If a small amount is given by intravenous infusion an obvious stimulation of respiration results, and this is followed, immediately after stopping the infusion, by a level somewhat above the resting value. In the case of a more rapid infusion of the same concentration of cyanide several different stages can be seen. First, there is a rapid rise in amplitude as well as a moderate increase in the respiratory rate; characteristic "gasps" occur at fairly regular intervals. In a second stage the respiratory activity is lowered, though the gasps become more frequent. After the infusion has ceased the respiration soon increases again, the picture now being rather a reflected image of the first part of the curve. After some time a third stage, with deep regular respiration sets in.

A comparison with the effects of carbon dioxide excess and oxygen want, respectively, reveals that the first stage resembles closely the results obtained during oxygen want and less those after carbon dioxide excess. The frequent occurrence of gasps and the insignificant alteration of the expiratory position are typical of the action of cyanide as well as of oxygen want. The second stage is very similar to the situation during pronounced oxygen want, when the respiratory centre is beginning to fail. It is also characteristic that oxygen want and cyanide infusion increase each other's effects, as found already by Geppert (1889) and confirmed by us. The maximal ventilation that can be obtained with cyanide is, however, about 15% higher than that during oxygen want. Evidently, therefore, most of the primary effect during cyanide infusion is due to oxygen want, but a small part is due to some other factor. The first stage of cyanide action on respiration disappears almost completely after section of the sinus nerves, a result which is in harmony with the view that it is mainly caused by oxygen want. That the second stage is due to the effect of oxygen want on the centre seems to be quite evident.

With regard to the third stage, however, it persists after denervation of the sinus nerves. It seems probable that in this case increased acidity of the blood is the stimulus responsible for the effect, a considerable and rapid rise in the lactic acid content of the blood and a rise in the hydrogen-ion concentration of the arterial blood having been found in connexion with intravenous injection of cyanide by Gesell, Krueger, Gorham, and Bernthal (1930). This also gives a satisfactory explanation of the fact that the primary increase in ventilation is somewhat greater in the first stage of cyanide infusion than that found during oxygen want alone. The continuous moderate rise in ventilation during and after the infusion in the denervated animal accords well with this explanation.

Effect of Lobeline

As already mentioned, lobeline stimulates respiration over the chemoreceptor mechanism. In this way intense action can be secured before the paralysing effect on the centre or on the sinus nerves appears. Consequently the total increase in ventilation which can be secured with

lobeline is much greater than in the case of oxygen want, when the deleterious effect on the centre relatively soon counteracts the stimulation from the chemoreceptors. Thus the total ventilation in a cat under the influence of 3 mg. of lobeline rose from the basal value of 0.93 to 3.52 l. a minute, whereas the maximal value during continuous oxygen want, found just before the curve began to fall again, was only 1.85 l. The total increase in ventilation in the former case thus was 2.6, in the latter case only 0.92 l. a minute (Euler, Liljestrand, and Zotterman, 1939a, 1939b).

Effect of Adrenaline

When injected intravenously in moderate doses adrenaline has two quite different actions on respiration. The first of these accompanies the rise in blood pressure and consists in a diminution of the depth and rate of breathing, which sometimes goes so far that an apnoea results. In view of the great interest attaching to this substance, the apnoea has been the object of much work and speculation.

Thus several authors have assumed a direct depression of the respiratory centre, but Schmidt (1929) has advanced convincing evidence against this hypothesis—for example, by demonstrating that a dose injected into the vertebral artery, which gives a relatively smaller rise in blood pressure than when given intravenously, also depresses respiration less. Roberts (1921) assumed that adrenaline causes a constriction of the vessels of the medulla, so that the centre is paralysed owing to want of oxygen or to an accumulation of metabolites. His own observation that an apnoea can be produced if the blood pressure is quickly raised by compression of the abdominal aorta indicates other possibilities, and Schmidt's finding that the cerebral blood flow is augmented when adrenaline is injected intravenously clearly contradicts his view. Schmidt came to the conclusion that reflex inhibition seems to be a factor, as vagotomy usually decreases the effect, but he considered the most important cause to be increased blood supply to the centre. At that time, however, the part played by the sinus mechanism in the respiratory function was unknown, and in view of this new knowledge it became necessary to reinvestigate the matter.

Experiments on dogs and cats, performed by Heymans and Bouckaert (1930) and by Wright (1930), proved that the adrenaline apnoea is mainly of reflex origin. If both vagi were cut and the carotid sinuses denervated, the action was practically abolished, only a very small effect remaining. According to Heymans and Bouckaert, the adrenaline apnoea is due to a reflex inhibition of the respiratory centre, produced by the increase in the blood pressure in the cardio-aortic and sinus circulatory areas. This explanation squares with the view held by Heymans and his school that a direct inhibitory influence on respiration is exercised from the baro-receptors. As already pointed out, we found no support for such an assumption. It seemed to accord better with the known facts to assume that the increased arterial blood pressure should afford a better blood flow through the carotid and aortic bodies and thereby diminish the stimulation of the chemoreceptors. As a matter of fact, Winterstein (1934–5) had pointed out that the decrease in ventilation after adrenaline injection already begins before the blood pressure starts to rise—it might even be falling—though the blood flow has increased. He concluded that the effect on respiration cannot be due to a reflex from the carotid sinus, but supposed that the explanation was to be sought either in the washing away of acid products or in a direct effect on the centre.

Gernandt, Liljestrand, and Zotterman (1945) found that the adrenaline apnoea could be prolonged if the animal was breathing oxygen; sometimes it also started a little later under these conditions. This seems to indicate a close connexion of the apnoea with the activity of the chemoreceptors. On the other hand, gas mixtures rich in carbon dioxide, as well as an injection of lobeline, could prevent the apnoea, which confirms that the centre is not paralysed. According to Heymans and Bouckaert and to Wright, only a very small decrease of respiration occurred after adrenaline if both vagi were cut and the sinuses were denervated. We further recorded the action potentials from the chemical fibres of the sinus nerve. There was a great reduction of impulses during adrenaline apnoea even during oxygen breathing. In this connexion the observation made by De Castro (1951) should be mentioned—namely, that the volume of the carotid body increased considerably after intravenous injection of adrenaline.

On recording the action potentials from the depressor nerve Gernandt (1946) found the same considerable reduction of small impulses after adrenaline as had been found earlier in the case of the sinus nerve. He also observed that if the chemoreceptors had been selectively eliminated by means of close intra-arterial injections of acetic acid, no apnoea occurred after adrenaline, though the pressoreceptors were still functioning. The same thing was seen by me in a cat in which the chemoreceptors of the carotid body had been eliminated by dissection. During oxygen want no increase in respiration was found and the blood pressure went down rapidly, but there was an excellent response of blood pressure to occlusion of the two common carotids, so that the pressoreceptors were intact. Adrenaline had hardly any immediate effect on respiration.

Our interpretation that the adrenaline apnoea is the result of a sudden elimination of the "chemoreceptor drive" (Bjurstedt, 1946) on respiration raised the question whether apnoea could be evoked by section of the sinus and vagus nerves. We found that section of the sinus nerves induces a reduction of respiration, and subsequent section of the vagi leads to slight apnoea. If the four buffer nerves are cut simultaneously an apnoea leading to the death of the animal results. The apnoea provokes oxygen want, and this causes a fall in the arterial blood pressure, as the depression of the vasomotor centre is not counteracted by the pressoreceptors. If the experiment was performed during oxygen breathing the usual rise in blood pressure due to the elimination of the inhibitory tone of the pressoreceptors occurred, and a short period of decreased respiration was observed. On the whole these experiences lend further support to the view that adrenaline apnoea is the consequence of a temporary elimination or reduction of the chemoreceptor activity.

The second effect of adrenaline on respiration appears when the blood pressure has again reached the normal level. A moderate increase in ventilation is then observed, which is probably due to the changed metabolism. As the respiratory quotient is usually somewhat increased a certain overventilation takes place. This seems to be sufficiently explained by the formation of lactic acid, which is a well-known consequence of the injection of adrenaline.

Effect of Acetylcholine

The last substance with which I propose to deal is acetylcholine. It has a complex action on respiration. As shown by Dautrebande and Maréchal (1933) and by Heymans, Bouckaert, Farber, and Hsu (1936), it stimulates the chemoreceptors. Schweitzer and Wright (1938) also demonstrated both stimulation and depression of respiration, which were to some extent independent of the chemoreceptors. In my experiments (Liljestrand, 1951) the effects of acetylcholine on the non-atropinized cat were compared with those of bleeding. It was found that small doses of acetylcholine stimulated respiration only indirectly owing to the oxygen want induced by the low blood pressure. With doses of 0.2 mg., however, there was also a direct stimulation of the chemoreceptors and a central inhibition as well as restriction of the amplitude of each respiration.

As is well known, atropinized cats stand much larger doses of acetylcholine, and these now cause a rise in blood pressure. A number of changes in respiration occur under these circumstances. After a brief expiratory apnoea, there is a short phase of increased breathing, followed by an apnoea of longer duration, which is interrupted by periodical respirations, and, finally, a period of regular breathing occurs again.

The initial apnoea is probably due to an inhibition of the respiratory centre, which is suddenly flushed by the drug. This view receives a certain support from the following observations: there is a simultaneous drop in the blood pressure, indicating an analogous effect on the vasomotor centre; after destruction of the carotid bodies the apnoea is prolonged and the blood pressure fall is more pronounced.

As has already been mentioned, the stimulating effect of acetylcholine is due to a reflex from the chemoreceptors. After intravenous injection of 0.7 ml. of 0.5/N ammonia hyperventilation due to oxygen want was greatly reduced and the blood pressure dropped suddenly. During the stimulating phase of acetylcholine the same dose of ammonia had no definite action on respiration, though a small drop in the blood pressure occurred. Similar results were found with carbaminoylcholine. These experiences tally well with the findings already quoted in respect of the action potentials.

The secondary apnoea is of a kind similar to that met with after adrenaline. If the centre is stimulated directly by carbon dioxide or indirectly by oxygen want the apnoea can be abolished. It comes a little later and is of somewhat greater duration than the adrenaline apnoea for the same rise in pressure, but this is to be expected as the result of the preceding period of stimulation. The action potentials in the chemical fibres of the sinus nerve disappear during the apnoea in the same way as after adrenaline. The periodical respiration following the apnoea is typical Cheyne–Stokes breathing resulting from overventilation and oxygen lack. It is abolished by oxygen.

Whether the increase in respiration after the periodicity is due to a direct stimulation of the centre—it is observed also after denervation—or to some indirect factor, has not been investigated.

The action of acetylcholine on the chemoreceptors is of special interest in respect of the question whether "drugs or changes in the blood which stimulate these nerve endings . . . produce their effects by liberation of acetylcholine as the chemical intermediary" (Schweitzer and Wright). The distribution of the nervous structures and their relations to the epithelioid cells of the carotid body are rather complicated, as demonstrated by De Castro (1951). The synapse corresponds to the glomus cell and its nervous end-plate. If this is taken as the point of attack of acetylcholine and related substances, hypoxia might influence them, as well as the thin sensory fibres, directly. Gesell, Brassfield, and Hamilton (1942) have pointed out that increased acidity induces anticholinesterase activity; hence the shift of reaction in the cell caused by ammonia might give rise to such a rapid splitting of the acetylcholine formed that it does not reach the concentration necessary to activate the neurone. In this way acetylcholine would be the common mediator for different types of stimulating agents in the carotid and aortic bodies.

Hollinshead and Sawyer (1945) have determined the cholinesterase and pseudo-cholinesterase activity of the carotid body of the cat. They found that the true cholinesterase activity was much lower for the carotid than for the superior cervical ganglion and about the same as for the non-synaptic sensory ganglia. As a rule the glomus contained more pseudo-cholinesterase than true cholinesterase. These findings are difficult to interpret, but they do not seem to be irreconcilable with the hypothesis that acetylcholine is the chemical mediator in the chemoreceptor mechanism.

It seems desirable that other ways should be tried in order to find out whether the hypothesis is well founded or not. Experiments carried out with the object of comparing the effects of oxygen want on respiration before and after intravenous injections of eserine or atropine led to no definite result. Sometimes eserine seemed to increase and atropine to reduce the effects, but the differences were small and irregular. Such experiments will also be difficult to interpret, for both drugs may act on many different structures. As acetylcholine itself affects the respiratory centre as well as the chemoreceptors, the results will depend on several factors. There is also every probability that the so-called synapses in the carotid body will not react to the low concentrations of the drugs which can be obtained by intravenous injection without causing serious general disturbances.

It therefore occurred to me that it might be better to treat the carotid bodies locally by applying small pieces of cotton soaked with solutions of the two substances mentioned. This method gave quite definite results. After eserine treatment the respirations became deeper and the decrease after oxygen was somewhat more pronounced than before. Oxygen want or carbon dioxide accumulation now induced greater responses than normally. The eserine salicylate was washed away and atropine sulphate applied. A reduction of the resting respiration followed, hardly influenced at all by oxygen-breathing. Carbon dioxide gave much less response than before treatment, and oxygen want had the typical effect observed after denervation—a continuous decrease, soon leading to a respiratory standstill. The pressor reactions showed similar variations, the greatest effect being met with after eserine, the smallest after atropine. The explanation is presumably the varying role of the chemoreceptors when the carotids are clamped.

The results speak strongly in favour of the hypothesis that acetylcholine is the chemical mediator in the carotid bodies.

The experiments thus afford another example of the correlation between physiology and pharmacology. In this case it has been possible, by studying the actions of drugs, to gain some insight into the normal processes going on in the body.

Summary

The discovery that the chemoreceptors of the carotid and aortic bodies when stimulated by oxygen want or carbon dioxide excess induce increased breathing made it desirable to investigate their role with regard to the action of certain drugs.

It was found that cyanides stimulate respiration mainly via the chemoreceptors, but also, especially in later stages, directly on the centre, probably through formation of lactic acid.

Moderate doses of lobeline act exclusively on the chemoreceptors, but the point of attack is central to that of oxygen want or carbon dioxide excess.

An intravenous injection of adrenaline leads to decreased respiration or even apnoea; this is due to the sudden elimination of the "chemoreceptor drive."

The same holds true for acetylcholine after atropinization, though there are differences which can be explained from the fact that acetylcholine also stimulates the carotid and aortic bodies in a similar way to lobeline. Before atropinization the stimulating effect of acetylcholine is enhanced by the simultaneous lowering of the blood pressure, which leads to oxygen want.

Local application of eserine to the carotid bodies increases the respiratory response to oxygen deficiency and carbon dioxide accumulation; the sensitivity of the chemoreceptors to these stimuli as well as to lobeline is abolished by local treatment with atropine. These results indicate that acetylcholine is the chemical mediator within the carotid body.

References

Bjurstedt, A. G. H. (1946). *Acta physiol. scand.*, **12**, Suppl. 38.
Bouckaert, J. J., Dautrebande, L., and Heymans, C. (1931). *Ann. Physiol. Physicochim. biol.*, **7**, 207.
Comroe, J. H., and Schmidt, C. F. (1938). *Amer. J. Physiol.*, **121**, 75.
Dautrebande, L., and Maréchal, R. (1933). *C.R. Soc. Biol., Paris*, **113**, 76.
De Castro, F. (1951). *Acta physiol. scand.*, **22**, 14.
Euler, U. S. v., and Liljestrand, G. (1936). *Skand. Arch. Physiol.*, **74**, 101.
—— —— (1937a). Ibid., **76**, 27.
—— —— (1937b). Ibid., **77**, 191.
—— —— (1940). *Acta physiol. scand.*, **1**, 93.
—— —— and Zotterman, Y. (1939a). *Skand. Arch. Physiol.*, **83**, 132.
—— —— —— (1939b). *Upsala LäkFören. Förh.*, **45**, 373.
Geppert, J. (1889). *Z. klin. Med.*, **15**, 208.
Gernandt, B. E. (1946). *Acta physiol. scand.*, **11**, Suppl. 35.
—— Liljestrand, G., and Zotterman, Y. (1945). Ibid., **9**, 367.
Gesell, R., Brassfield, C. R., and Hamilton, M. A. (1942). *Amer. J. Physiol.*, **136**, 604.
—— Krueger, H., Gorham, G., and Bernthal, T. (1930). Ibid., **94**, 300, 339.
Haldane, J. S., and Priestley, J. G. (1935). *Respiration*, 2nd ed., p. 493. Oxford.
Hering, H. E. (1927). *Die Karotissinusreflexe auf Herz und Gefässe*, p. 150. Leipzig and Dresden.
Heymans, C., and Bouckaert, J. J. (1930). *J. Physiol.*, **69**, 254.
—— —— and Dautrebande, L. (1930). *Arch. int. Pharmacodyn.*, **39**, 400.
—— —— Farber, S., and Hsu, F. Y. (1936). Ibid., **54**, 129.
Heymans, J. F., and Heymans, C. (1927). Ibid., **33**, 273.
Hollinshead, W. H., and Sawyer, C. H. (1945). *Amer. J. Physiol.*, **144**, 79.
Liljestrand, G. (1951). *Acta physiol. scand.* In press.
Roberts, Ff. (1921). *J. Physiol.*, **55**, 346.
Samaan, A., and Stella, G. (1935). Ibid., **85**, 7P.
Schmidt, C. F. (1929). *J. Pharmacol.*, **35**, 297.
Schweitzer, A., and Wright, S. (1938). *Quart. J. exp. Physiol.*, **28**, 33.
Winterstein, H. (1934–5). *Pflüg. Arch. ges. Physiol.*, **235**, 377.
Wright, S. (1930). *J. Physiol.*, **69**, 493.

NEURAL CONTROL OF THE PITUITARY GLAND: II. THE ADENOHYPOPHYSIS

WITH SPECIAL REFERENCE TO THE SECRETION OF A.C.T.H.*

BY

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As described previously, only two endocrine glands—the adrenal medulla and neurohypophysis—have a secretomotor nerve supply and are dependent on this supply for normal function. The adenohypophysis (anterior pituitary gland), thyroid, adrenal cortex, ovaries, and testes lack a well-defined innervation. It has been known for many years, however, that these latter glands are influenced by nervous processes—the evidence for this statement has been reviewed (Harris, 1948a) — but the mechanism whereby such an influence is exerted was uncertain. The position would be clarified if it could be found how the adenohypophysis is brought under neural control; for the thyroid, adrenal cortex, and gonads would then be indirectly under similar control via the action of the anterior pituitary eutrophic hormones. Some such sequence of events as illustrated in Fig. 1 may be envisaged. Stimuli arising in the external environment, such as changes in exposure to light or temperature or exposure to a variety of conditions grouped under the heading "stress," are reflected by changes in activity in various parts of the central nervous system. These changes, and those arising from mental and psychological upsets, may affect the secretory activity of the adenohypophysis by means of structures in the hypothalamus and pituitary stalk.

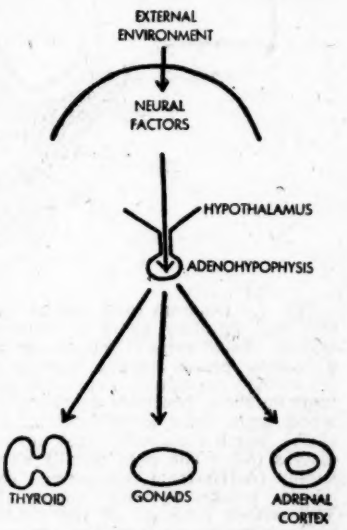

FIG. 1.—Diagram to illustrate a possible mechanism whereby the activity of the anterior pituitary gland, thyroid, adrenal cortex, and gonads may be modified by changes in the external environment or in the central nervous system (psychological or emotional upsets). It seems likely that such changes may affect anterior pituitary secretion via the hypothalamus, and through the intermediation of the thyrotrophic, adrenocorticotrophic, and gonadotrophic hormones may thus affect also the activity of the thyroid gland, adrenal cortex, and gonads.

Anatomical Links Between the Central Nervous System and the Adenohypophysis

Nervous

Three nervous pathways have been described as passing from the central nervous system to the adenohypophysis; branches from the cervical sympathetic

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chain, the parasympathetic fibres of the greater superficial petrosal branch of the facial nerve, and the hypothalamo-hypophysial tract of the pituitary stalk. Section of these various pathways, however, is compatible with normal function of the adenohypophysis and does not necessarily prevent neural processes from affecting anterior pituitary function. Microscopical examination of the adenohypophysis also throws serious doubt on the functional significance of these possible nerves of supply, for most workers have found few, if any, nerve fibres present in the greater part of the anterior lobe of the pituitary gland.

Neurovascular

Many years ago Professor Fr. I. Rainer, of Bucharest, noticed prominent blood vessels running along the human pituitary stalk, and suggested that one of his pupils (later

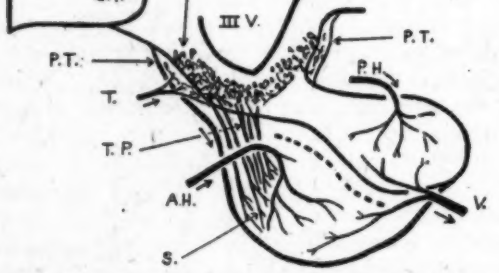

FIG. 2.—Diagram of a sagittal section through the hypothalamus and pituitary gland to illustrate the hypophysial vascular system. Small twigs (T.) from the internal carotid arteries supply a vascular plexus situated between the pars tuberalis (P.T.) and the median eminence. From this plexus sinusoidal loops (L.), in large numbers, penetrate the tissue of the median eminence. The blood from these loops is drained by the large portal trunks (T.P.), which eventually break up into the sinusoids of the pars distalis (S.). The pars distalis also receives a systemic arterial supply (A.H.) from the internal carotid artery, and the infundibular process a similar supply (P.H.) from the same source. The venous drainage of the pituitary gland is by wide short veins into the surrounding venous sinuses (V.). O.T.=optic tract; III V.=third ventricle. (By kind permission of the Royal Society of Medicine.)

Professor G. T. Popa) should examine them in detail. Popa made serial sections through the hypophysis, still in connexion with the diencephalon, and observed that the prominent vessels of the stalk were in reality portal vessels ending in capillaries at both ends, in the tuber cinereum above and in the hypophysis below. These observations remained unpublished until, at the suggestion of Professor G. Elliot-Smith, the anatomy of these structures was again investigated at University College, London. Popa and Fielding (1930, 1933) then made their first reports on the "hypothalamo-hypophysial portal vessels." They suggested that blood flowed from the pituitary gland up the vessels and was redistributed in the hypothalamus.

The main anatomical features of the vessels were confirmed by Wislocki and King (1936) and Wislocki (1937, 1938). According to these workers, however, the capillaries at the superior end of the portal vessels were situated in the median eminence of the tuber cinereum (then recognized as part of the glandular neurohypophysis and not hypothalamus proper). Therefore they denied the existence of a hypothalamo-hypophysial portal system, and renamed the vessels the hypophysial portal vessels on the grounds that the whole extent of the vessels was intrinsic to the hypophysis. One unfortunate consequence of this correction in terminology was the general belief that the hypothalamo-hypophysial portal vessels had been "disproved." From the histological evidence Wislocki drew the conclusion that the direction of blood flow in these vessels was in a direction *towards* the pituitary gland. Green and Harris (1947) reinvestigated the region in a variety of mammals, and largely confirmed the findings of Wislocki. The vascular pattern of the adenohypophysis may be compared to that of the liver in that it has a systemic arterial supply (a small branch from the internal carotid artery), a portal supply (the hypophysial portal vessels), and a systemic venous drainage (short wide veins passing laterally to the surrounding venous sinuses) (see Fig. 2).

The pathway of the portal blood is as follows. Small twigs from the internal carotid arteries and posterior communicating arteries run to supply a rich vascular plexus in the pars tuberalis. From this plexus arises a multitude of wide capillary loops which penetrate into the tissue of the median eminence, where they come into intimate relationship with the nerve fibres of the hypothalamo-hypophysial tract. The blood from these loops is drained into the large portal trunks which pass down the pituitary stalk and redistribute the blood into the capillaries and sinusoids of the anterior pituitary gland. Green (1947, 1948, 1949) has made a thorough investigation of the portal vessels in many types of vertebrates, and finds a similar system of vessels in all forms examined, from amphibians to man. Microscopical examination of these vessels in living forms has established that the direction of blood flow is *from* the median eminence *to* the tuber cinereum. (Amphibians: Houssay, Biasotti, and Sammartino, 1935; Green, 1947. Mammals: Green and Harris, 1949.)

In view of the above anatomical facts it was suggested (Harris, 1944; Green and Harris, 1947) that the hypothalamus may influence the secretion of the adenohypophysis by means of a neurovascular link—for example, that hypothalamic nerve fibres end in close relation to the capillary loops in the median eminence, and, on excitation, liberate some chemotransmitter into these vessels, this substance being transported by the portal vessels to excite or inhibit the pars distalis of the gland.

Hypothalamic Control of Anterior Pituitary Function

To investigate the hypothesis that the hypothalamus regulates anterior pituitary secretion by a neurovascular mechanism an attempt was made to analyse some of the factors underlying gonadotrophic secretion. For this purpose the rabbit was chosen as the experimental animal. It is well known that in the rabbit the stimulus of coitus excites the adenohypophysis by means of a nervous reflex to secrete gonadotrophic (luteinizing) hormone, and that ovulation thereby occurs some ten hours after mating. On the supposition that one part of the path of the nervous reflex involved the hypothalamus, this structure and various parts of the pituitary gland were subjected to localized electrical stimulation in a number of unanaesthetized rabbits (Harris, 1948b).

The method used was that of remote control stimulation as described previously (Harris, 1951). It was found that stimulation of the tuber cinereum, particularly the posterior part, might be effective in causing a full ovulatory response after as short a stimulus as three minutes. Similar stimulation, however, applied direct to the pars distalis, pars intermedia, or infundibular stem of the pituitary gland for as long as seven

and a half hours produced no sign of activation of the ovaries. Assuming that the only tissues in this region which are sensitive to electrical stimulation are nerve fibres (and this would seem probable—cf. the results obtained by Cannon and Rosenblueth (1937), who studied the effect of electrical stimulation of the denervated adrenal medulla), then these results are explicable on the idea of neurovascular transmission (see Fig. 3).

It seems likely that stimulation of the tuber cinereum excites nerve fibres normally involved in the ovulatory reflex, and that the negative results of stimulating the pituitary stalk and gland are due to the stimulus being transmitted humorally in these structures. It may be argued that the mechanism of ovulation in the rabbit is specialized and that results obtained from its study are not of general application. However, in a few rabbits it was found that prolonged stimulation of the tuber cinereum by the same method resulted in a glycotrophic response—that is, a marked decrease in sensitivity to small doses of insulin (Harris, 1951, unpublished observations).

Another approach to the problem of control of gonadotrophic secretion involved sectioning the pituitary stalk. The results of stalk section on reproductive function, as reported in the literature, are very discordant. After performing this operation on the rat, Dempsey and Uotila (1940) and Dempsey and Searles (1943) found that some animals exhibited normal reproductive processes, Richter (1933) found that oestrous cycles were prolonged, while Westman and Jacobsohn (1938a, 1938b) and Brolin (1945) reported gonadal atrophy. Equally discordant results have been reported by workers who have studied the effects of stalk section on other pituitary functions. It is difficult to explain these varied results if the effects of pituitary stalk section are held to be due to sectioning the nerve fibres of the stalk, as these nerve fibres do not regenerate after they are cut. If normal anterior pituitary activity is dependent on the hypophysial portal vessels, however, the discrepancies reported after stalk section might be due to variations in the degree of regeneration of these vessels.

Differences in the operative techniques used by different workers—such as the distance the two ends of the cut stalk are separated at operation—might account for variations in vascular regeneration. To investigate this possibility a temporal approach to the pituitary stalk region of the rat was devised and the stalk sectioned in a series of animals (Harris, 1950). The reproductive processes (oestrous cycles and pseudopregnancy response to sterile coitus) were observed in these animals, after which they were killed and their vascular systems perfused with an indian-ink solution. A study of serial sections through the hypothalamus, pituitary gland, and base of skull of these rats revealed (*a*) that regeneration of the hypophysial portal vessels did occur in the majority of animals operated on in this way, and (*b*) that such regeneration could be correlated with the post-operative return of oestrous cycles and pseudopregnant responses to sterile coitus.

In a further series of animals it was demonstrated that the insertion of a foreign body (usually a small plate of paper) between the cut ends of the pituitary stalk would prevent regeneration of the portal blood vessels, and that in these rats the ovaries and reproductive tract underwent atrophy. It should be mentioned that cutting the pituitary stalk inevitably disturbs the vascular supply of the gland, but in the above experiments there was no correlation between the amount of anterior pituitary tissue in the animal, or the richness of the vascular bed of this tissue, and the post-operative return of reproductive activity. It was concluded that the return of anterior pituitary function after stalk section is dependent on regeneration of the hypophysial portal vessels across the site of section. The portal vessels of the monkey have been observed to regenerate in a similar manner (Harris and Johnson, 1950).

A striking feature of anterior pituitary tissue, reported by many workers, is the inability of such tissue to maintain normal function when transplanted to a distant site in the body of the hypophysectomized animal. Other endocrine glands, such as the thyroid, parathyroids, ovaries, testes, and adrenal cortex, may regain normal function after transplantation. One possible explanation of this difference is that the thyroid, gonads, and adrenal cortex depend on a supply of pituitary

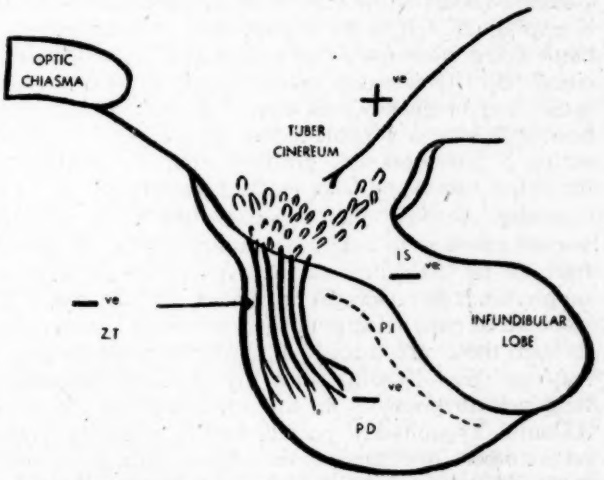

FIG. 3.—Diagram of a sagittal section through the hypothalamus and pituitary gland of a rabbit. Electrical stimulation of the tuber cinereum is effective in causing release of gonadotrophic hormone from the pars distalis of the pituitary gland, whereas similar stimulation applied direct to the gland—to the infundibular stem (I.S.), pars intermedia (P.I.), pars distalis (P.D.), or zona tuberalis (Z.T.)—is ineffective.

eutrophic hormone, carried in the general systemic circulation, for their normal activity. Therefore transplantation does not remove them from the field of their normal stimulus. If, however, the anterior pituitary gland is dependent on a humoral excitant carried by the local circulation of the hypophysial portal vessels, then transplantation to the spleen, anterior chamber of the eye, or other sites would remove it from its physiological stimulus.

In collaboration with Dr. Dora Jacobsohn, of the University of Lund (Harris and Jacobsohn, 1951), it was decided to hypophysectomize a series of rats and to graft anterior pituitary tissue into the subarachnoid space under the tuber cinereum. In this way it was possible to check the completeness of hypophysectomy (after death) by examination of serial sections through the empty hypophysial capsule, but yet to place the grafted tissue near the median eminence and the cut hypophysial portal vessels so that regeneration of the vessels into the grafted tissue might occur. Control experiments were performed in the same way, except that the grafts were placed in the subarachnoid space under the temporal lobe of the brain. It was seen that

the grafts placed under the tuber cinereum became revascularized by the portal vessels of the median eminence, and in the majority of these cases normal anterior pituitary function was regained by the grafted host. Normal function was demonstrated by regular oestrous cycles, pregnancy, and milk secretion, the weights of the ovaries and adrenal glands being within the normal range, and a normal histological picture for the ovaries, thyroid, and adrenal cortex.

Microscopical examination showed that the control animals with " temporal lobe grafts " had as much viable anterior pituitary tissue, which was as well vascularized, as in the animals that had the graft placed under the median eminence. In the control group, however, the graft was not vascularized by the portal vessels. In these animals, also, there were no oestrous cycles, and the ovaries, thyroid, and adrenal glands were atrophic. It would seem that anterior pituitary grafts that become revascularized by the hypophysial portal vessels may regain normal activity, but grafts vascularized only by systemic vessels show very reduced functional activity, if any at all. It is of interest that anterior pituitary tissue taken from male rats and placed under the tuber cinereum of female rats would support normal oestrous cycles and pregnancy, and that tissue taken from newborn rats would support adult reproductive functions within a few weeks of grafting—that is, long before the donor rats would have reached puberty.

Strong evidence, then, supports the view that the normal stimulus to anterior pituitary activity is derived from the hypothalamus via the hypophysial portal blood supply, and that changes in activity of the gland (in response to external stimuli such as coitus) are mediated through these structures. A similarity could be drawn between the hypothalamus/hypothalamo-hypophysial tract/neurohypophysis on the one hand and the hypothalamus/hypophysial portal vessels/adenohypophysis on the other. In both cases the activity of the gland ceases or is seriously impaired if separated from the hypothalamus, and probably in both cases the hypothalamus is involved in the adjustments of secretory activity necessary to integrate pituitary function with the requirements of the organism as a whole.

There is little evidence regarding the details of the mechanism by which the hypophysial portal vessels affect activity of the adenohypophysis. On the grounds that a sympatholytic drug (dibenamine) blocks the ovulatory reflex in the rabbit, and other evidence, Markee, Sawyer, and Hollinshead (1948) and Sawyer, Markee, and Townsend (1949) suggest that the portal vessels transmit an adrenergic substance which stimulates the release of the luteinizing hormone from the anterior pituitary gland. Evidence of a similar nature has been adduced also for the rat (Sawyer, Everett, and Markee, 1949; Everett, Sawyer, and Markee, 1949; Everett and Sawyer, 1949).

One question that follows from the above argument is whether each of the six " hormones " secreted by the anterior pituitary gland requires the supposition of a separate humorally transmitted excitor substance. Although it is possible, by chemical extraction, to separate six " hormones " from anterior pituitary tissue, very little data are available to show how the substances enter the blood stream. It is possible that they reach the blood as six separate substances, but it is also possible that two or more are linked together as different fractions of a larger molecule.

Control of the Secretion of the Adrenocorticotrophic Hormone

In view of the important advances being made in the field of clinical medicine regarding the treatment of a variety of conditions with the adrenocorticotrophic hormone (A.C.T.H.), the investigation of the factors underlying the normal secretion of this hormone have received much attention in the laboratory. There are two sides to this problem. First, the means by which a steady secretion of A.C.T.H. is maintained in the normal animal under optimum conditions; and, secondly, the mechanisms employed in producing increased secretion under conditions of stress. The same factors may be involved in both cases, but it is possible that stress stimuli may activate one or more additional mechanisms.

A.C.T.H. maintains the structure and function of the adrenal cortex. Since accurate assays of the blood level of A.C.T.H. cannot yet be made, the rate of secretion of this hormone has to be measured indirectly. The criteria which have been most used in the investigation of the factors controlling A.C.T.H. release are (1) the effects of A.C.T.H. on the size, weight, and histology of the adrenal cortex, and on the cholesterol and ascorbic acid content of the adrenal cortex; and (2) the effect of an increased secretion of the adrenal cortex as shown by a fall in blood lymphocytes or eosinophils (see Fig. 4). The validity of these methods, and others, has been discussed by Sayers (1950) in a detailed review.

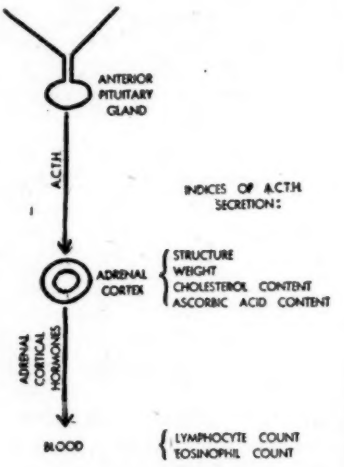

FIG. 4.—The structure, weight, and cholesterol and ascorbic acid content of the adrenal cortex bear an immediate relationship to the blood level of A.C.T.H., whereas the lymphocyte and eosinophil counts are related to the blood level of the adrenal cortical hormones, which in turn reflects the level of A.C.T.H.

At the present time three views, not necessarily incompatible, have been put forward concerning the regulation of A.C.T.H. release: (1) A.C.T.H. secretion is regulated by the systemic blood level of adrenaline; (2) A.C.T.H. secretion is regulated by the systemic blood level of the adrenal cortical hormones; (3) A.C.T.H. secretion is controlled by the hypothalamus acting through the hypophysial portal vessels. These three views will be discussed in turn.

1. Systemic Blood Level of Adrenaline

In 1944 Vogt found that an intravenous infusion of adrenaline causes an immediate and large increase in the rate of secretion of the adrenal cortex. At first it was considered likely that adrenaline exerted a direct effect on the cells of the adrenal cortex, but the findings of Long and Fry (1945) that depletion in adrenal cholesterol and ascorbic acid follow injection of adrenaline in the normal but not in the hypophysectomized animal threw doubt on this interpretation.

It seems clear that the major influence of adrenaline in exciting the adrenal cortical secretion is mediated in some way through the pituitary gland, though the question of whether adrenaline exerts any action directly on the adrenal cortex is unsettled (Pickford and Vogt, 1951).

Long (1947) stated that stimulation of the autonomic system with the concomitant release of adrenaline, which occurs under a variety of conditions, appears to be a major factor in the activation of A.C.T.H. secretion from the anterior pituitary gland. This view might be expressed diagrammatically as in Fig. 5. The data on which this view is based are given by Gershberg, Fry, Brobeck, and Long (1950), and McDermott, Fry, Brobeck, and Long (1950a). Infusions of small doses of adrenaline which appear to be within the physiological range produce a fall in the level of adrenal ascorbic acid in the normal but not in the hypophysectomized rat. Conditions of stress, which have been known for many years to be associated with increased activity of the autonomic system and adrenaline liberation, cause a fall in the adrenal content of cholesterol and ascorbic acid in the normal but not in the hypophysectomized rat.

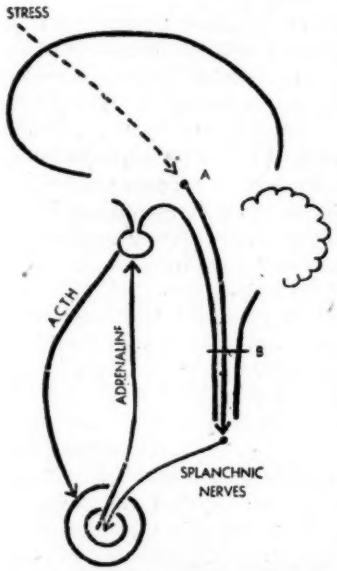

FIG. 5.—Diagram illustrating the views of Long and his colleagues. Stimulation of the autonomic system with concomitant release of adrenaline, which occurs under a variety of conditions of stress, is believed to be a major factor in the activation of A.C.T.H. secretion from the anterior pituitary gland. A = the hypothalamic level. B = the spinal level.

In order to see if there is a causal relationship between adrenaline and A.C.T.H. liberation in response to stress, Long and his colleagues have investigated the effect of stress after demedullation of the adrenal glands, and after interrupting the neural pathway responsible for adrenaline secretion at the hypothalamic (A, Fig. 5) or spinal (B, Fig. 5) level. They found that adrenal-demedullated rats no longer responded to mild stress stimuli (stimulation of an afferent nerve trunk for 15 minutes), but such rats still showed a marked response to more severe stress (fasting plus exposure to cold for four hours, haemorrhage, or laparotomy). Rats with the spinal cord sectioned at the level of the third thoracic vertebra behaved in a similar way, in that a mild pain stimulus (injection of hypertonic saline beneath the skin of the scalp) no longer resulted in A.C.T.H. release, but more severe stress (cold) produced a marked response. Also, rats with diencephalic lesions still reacted to laparotomy by releasing A.C.T.H., as shown by an eosinopenic response.

A study of the time relations of these responses showed that the rats in which adrenaline release was prevented had a longer latency in the secretion of A.C.T.H. to stress. Normal animals responded to stress by a marked release of A.C.T.H. within one hour of the stress, and the response was maximal at the fourth hour. The animals in which adrenaline secretion was prevented showed no response at one hour but a normal response at the fourth hour after stress. For this reason Long and his colleagues suggested that a double mechanism underlies the secretion of A.C.T.H. following stress: (*a*) a quick autonomic mechanism depending on reflex secretion of adrenaline which activates the anterior pituitary; and (*b*) a slower metabolic mechanism which is not dependent on adrenaline secretion and which is therefore not abolished by adrenal demedullation or denervation.

In an attempt to localize the site of action of adrenaline in producing A.C.T.H. release McDermott, Fry, Brobeck, and Long (1950b) transplanted anterior pituitary tissue to the anterior chamber of the eye in hypophysectomized rats. Definite eosinopenic responses occurred in these animals following subcutaneous injection of adrenaline or injection of adrenaline into the eye containing the graft (but not into the normal eye). The conclusion drawn from these experiments is that adrenaline may cause A.C.T.H. secretion by a direct action on anterior pituitary cells. It is perhaps significant that the pituitary transplants of these animals did not prevent partial adrenal atrophy or complete atrophy of the testes and did not maintain body growth.

The general view, upheld by Long and his colleagues, that adrenaline secretion is part of a physiological mechanism underlying A.C.T.H. release in response to stress, is open to question. The completely sympathectomized animal may resist many forms of stress almost as well as do intact animals (see discussion by Sayers, 1950). Hume and Wittenstein (1950) found that electrical stimulation of the hypothalamus of dogs resulted in an eosinopenia that was not altered by total sympathectomy, and Colfer, de Groot, and Harris (1950) observed that the lymphopenic response which followed a mild pain stimulus in rabbits did not differ from the response obtained with the adrenal glands denervated.

Recently Fortier (1950) showed that audiogenic stimulation (sound) of normal rats produces a rapid and intense discharge of A.C.T.H. The response to this sensory stimulus was not affected by removal of the adrenal medulla. Vogt (1951) also found that mild stress stimuli (emotional in type) still produce a fall in adrenal ascorbic acid after adrenal demedullation. This fall was not so large as in normal rats, but, contrary to the results of Long and his co-workers, did occur within the course of one hour. Vogt concludes: "... The secretion from the adrenal medulla is an important but not the only cause for the adrenocortical response to emotion." Sayers (1950) suggested the possibility that adrenaline may act by promoting the tissue utilization of adrenal cortical hormones, thus lowering the blood level of these substances and producing increased A.C.T.H. output.

2. Systemic Blood Level of Adrenal Cortical Hormones

The view that A.C.T.H. secretion from the anterior pituitary gland is regulated by the blood level of the adrenal cortical hormones has been described in detail by Sayers (1950), and reference should be made to this work for a detailed discussion. The evidence in support of Sayers's view may be summarized as follows. Chronic administration of adrenal cortical extracts or desoxycorticosterone (deoxycortone B.P.) acetate to normal animals results in adrenal atrophy, presumably by causing decreased secretion of A.C.T.H. from the animal's

own pituitary gland. Deoxycortone acetate will prevent the adrenal hypertrophy that normally follows the application of a variety of non-specific damaging agents.

In acute experiments Sayers and Sayers (1947) showed that the drop in adrenal ascorbic acid which normally follows the application of cold or heat, or the injection of typhoid toxin, adrenaline, or histamine, can be prevented by the pretreatment of the animal with adrenal cortical extract or crystalline cortical steroids. Since the effect of injected A.C.T.H. is not modified by administration of adrenal cortical extracts they believe that the cortical substances act by inhibiting the release of A.C.T.H. from the pituitary gland. A quantitative relationship has also been found to exist between the dose of cortical steroid administered and the degree of inhibition of A.C.T.H. release in response to stress (Sayers and Sayers, 1948). It is concluded that stress stimuli increase, in some way, the utilization of adrenal cortical hormones by the peripheral tissues. The blood level of these hormones falls, and this fall stimulates anterior pituitary cells to liberate increased amounts of A.C.T.H. Similarly an increase in blood level of adrenal cortical hormones is thought to inhibit A.C.T.H. secretion. According to this view, then, the anterior pituitary/adrenal cortex forms a self-regulating system, the balance of which is broken mainly by variations in activity of the peripheral tissues (see Fig. 6).

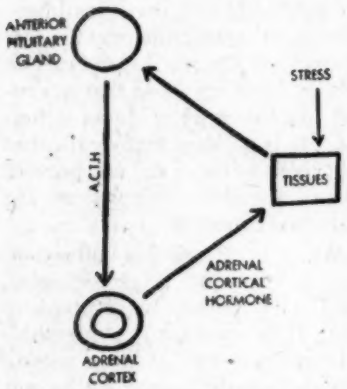

FIG. 6.—Diagram illustrating the view of Sayers that the secretion of A.C.T.H. by the anterior pituitary gland is regulated by the blood level of adrenal cortical hormones. Stress is thought to act direct on the tissues, increasing the tissue utilization of the adrenal cortical hormones, so that the level of these substances in the blood supplying the pituitary gland is lowered, thereby increasing the output of A.C.T.H.

It is difficult, however, to believe that the blood level of adrenal cortical hormones is the only factor which regulates the secretion of A.C.T.H. For example, blood from the aorta eventually supplies both the peripheral tissues and the pituitary gland. Therefore under conditions of prolonged stress the peripheral tissues could not receive an increased supply of adrenal cortical hormones, for the pituitary gland would also receive the same increased supply, which would in turn reduce the output of A.C.T.H. and so of adrenal cortical hormones.

Cheng, Sayers, Goodman, and Swinyard (1949) found that hypophysectomized rats bearing intraocular or intrasplenic grafts of anterior pituitary tissue responded to histamine stress (intravenous injection of small doses of histamine) with a fall in the level of adrenal ascorbic acid. The results were interpreted to mean that neural or vascular connexions between the hypothalamus and anterior pituitary are not essential for the immediate discharge of A.C.T.H. in acute stress. However, the physiological significance of these results is open to doubt, for the adrenal glands of the rats bearing pituitary grafts were as atrophic in most cases as in the hypophysectomized control animals without grafts. It would appear that the natural stimulus of the animal's own need for increased A.C.T.H. secretion was insufficient to increase the activity of the graft (an activity which *could* be increased, as shown by the effects of histamine).

It is felt that the evidence is conclusive that the blood level of the adrenal cortical hormones influences the rate of secretion of A.C.T.H., though the manner in which this occurs is obscure. It is doubtful whether this is a direct action on the cells of the adenohypophysis.

3. Hypothalamic Control

In view of the strong evidence that the hypothalamus plays a prominent part in controlling the secretion of the gonadotrophic hormones, an investigation was undertaken to see whether a similar mechanism regulated the output of A.C.T.H.

In preliminary experiments (Colfer, de Groot, and Harris, 1950) it was shown that rabbits behave as other animals, in that emotional stress stimuli (restraint or subcutaneous faradism) evoke a lymphopenia. Hypophysectomy abolished this response to stress, though injection of A.C.T.H. was still followed by a lymphopenia in the hypophysectomized animal. There was then available for investigation a reaction which could be indicated : emotional stress → anterior pituitary gland → adrenal cortex → lymphopenia. To see whether A.C.T.H. secretion could be evoked by hypothalamic stimulation, de Groot and Harris (1950) used the remote-control technique, with the primary coil enlarged to surround the cage containing the animal. Thus the animal was not subjected to concurrent emotional stress during the periods of stimulation. It was found that stimulation of the posterior region of the tuber cinereum or mammillary body resulted in a lymphopenia that was similar in time relations and magnitude to that following an emotional stress stimulus or intravenous injection of an appropriate dose of A.C.T.H. Stimulation of other regions in the hypothalamus (including the supraoptico-hypophysial tract) and pituitary gland (pars and zona tuberalis, pars distalis, pars intermedia, and infundibular stem) did not elicit the response.

Results which are in the main similar to these have been obtained by Hume and Wittenstein (1950) by stimulating the hypothalamus of the unanaesthetized dog. The effect of electrolytic lesions placed in the hypothalamus or pituitary gland was also studied (de Groot and Harris, 1950). It was found that in two rabbits in which the zona tuberalis (the part of the anterior pituitary gland of the rabbit traversed by the hypophysial portal vessels) was destroyed, and in other animals in which the posterior part of the tuber cinereum or mammillary body was damaged, the lymphopenic response to stress was diminished or abolished. It was concluded that the secretion of A.C.T.H. which follows an emotional stress stimulus in the rabbit is regulated by the hypothalamus acting via the hypophysial portal vessels.

Results which lend strong support to this view come from the experiments of Harris and Jacobsohn (1951) on pituitary grafts in hypophysectomized rats. As mentioned above, it was found that if anterior pituitary tissue was placed under the tuber cinereum of the hypothalamus in hypophysectomized rats the graft became revascularized by the hypophysial portal vessels, and normal function was regained in the majority of animals. The adrenal glands of these animals were within the normal range as regards weight and structure.

In control animals in which similar grafts were placed elsewhere in the subarachnoid space, although the grafts were viable and richly vascularized (but not by the hypophysial portal system), the adrenal glands underwent marked atrophy. It is felt that these results are highly significant with regard to the mechanism of A.C.T.H. secretion under non-stress conditions. The adrenal atrophy reported by Cheng *et al.* (1949), McDermott *et al.* (1950b), and many other previous workers in hypophysectomized rats bearing pituitary grafts in the anterior chamber of the eye and other sites stand in marked contrast to the above results.

Conclusions Regarding Control of A.C.T.H. Secretion

The evidence derived from studies of pituitary transplants and grafts shows that the basic steady output of A.C.T.H. by the anterior pituitary gland is largely dependent on this gland's anatomical relationship with the hypothalamus. The same data also show that the structures connecting the hypothalamus and adenohypophysis which are of importance in maintaining normal A.C.T.H. liberation are the hypophysial portal vessels. It is likely that under optimum conditions the blood level of adrenal cortical hormones exerts a fine control of A.C.T.H. output. It is felt probable, however, that this control is mediated via the hypothalamus, since the adrenal atrophy (and presumably decreased level of the adrenal cortical hormones in the blood) is not effective in maintaining A.C.T.H. output in rats that have had the anterior pituitary gland transplanted to a site remote from the hypothalamus. These views are expressed diagrammatically in Fig. 7. Analogy might be drawn to the respiratory mechanism, where the act of respiration is basically dependent on the nervous system but modified by the carbon dioxide content of the blood supply to the respiratory centre.

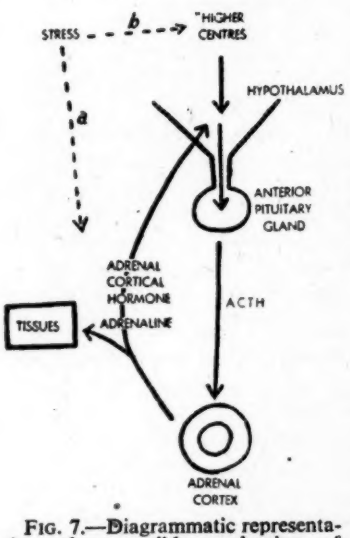

FIG. 7.—Diagrammatic representation of a possible mechanism of control of A.C.T.H. secretion. Under optimal, quiescent conditions it is believed that the basal output of A.C.T.H. is under hypothalamic control mediated by the hypophysial portal vessels of the pituitary stalk. According to the type of stress, this basal output may be increased either by (*a*) an effect on the blood level of adrenal cortical hormones and adrenaline, or (*b*) an effect mediated via the hypothalamus and pituitary stalk. On the data available it is thought likely that the blood level of adrenal cortical hormones and adrenaline affect anterior pituitary activity via the hypothalamus, and not by an action directly on anterior pituitary cells.

The factors involved in the increased secretion of A.C.T.H. in response to stress stimuli probably vary according to the type of stress. The work of Fortier (1951, personal communication) is of much interest in this respect. Fortier exposed groups of normal rats, and hypophysectomized rats with anterior pituitary transplants in the eye, to varied types of stress stimuli: (*a*) systemic (adrenaline, cold, histamine); (*b*) emotional (immobilization); and (*c*) sensory (sound) stimuli. It was found that adrenaline, cold, and histamine brought about a definite eosinopenia in both normal and grafted animals, but that sound and immobilization induced a marked fall of the eosinophils in the intact but none in the grafted animals. Fortier suggests that these results indicate a dual regulation of A.C.T.H. release—one purely humoral in response to systemic stress stimuli, and the other probably neuro-humoral mediated by the hypothalamo-hypophysial neurovascular pathway, and coming into play under the influence of nervous or emotional stimuli. These two mechanisms might be indicated by *a* and *b* in Fig. 7.

The views expressed above regarding the factors regulating A.C.T.H. secretion are similar to those regarding control of gonadotrophic secretion. There can be little doubt that the normal output of gonadotrophin and the maintenance of oestrous cycles and other reproductive processes is dependent on hypothalamic control of the anterior pituitary gland acting via the portal blood vessels. The evidence indicates that the secretion of the gonads reacts back on to the hypothalamus (Everett and Sawyer, 1949; Harris, 1950), and that emotional and environmental stimuli modify gonadotrophin secretion by an action mediated through the hypothalamus. A point of interest in this connexion is that barbiturate drugs, which are known to have a selective action upon the hypothalamus (Masserman, 1937), also appear to block, at least partially, the release of A.C.T.H. (Sayers and Sayers, 1948; Hume and Wittenstein, 1950) and of the luteinizing hormone (Everett and Sawyer, 1950).

I am grateful to Miss M. Vogt, Edinburgh, and Dr. C. Fortier, Montreal, for allowing me to quote from their unpublished results.

REFERENCES

Brolin, S. E. (1945). *Acta anat., Basel*, Suppl. 3, p. 165.
Cannon, W. B., and Rosenblueth, A. (1937). *C.R. Soc. Biol., Paris*, **124**, 1262.
Cheng, C. P., Sayers, G., Goodman, L. S., and Swinyard, C. A. (1949). *Amer. J. Physiol.*, **159**, 426.
Colfer, H. F., Groot, J. de, and Harris, G. W. (1950). *J. Physiol.*, **111**, 328.
Dempsey, E. W., and Searles, H. F. (1943). *Endocrinology*, **32**, 119.
—— and Uotila, U. U. (1940). Ibid., **27**, 573.
Everett, J. W., and Sawyer, C. H. (1949). Ibid., **45**, 581.
—— —— (1950). Ibid., **47**, 198.
—— —— and Markee, J. E. (1949). Ibid., **44**, 234.
Fortier, C. (1950). *Proc. Canad. physiol. Soc.*, 14th Ann. Meeting, October, 1950.
Gershberg, H., Fry, E. G., Brobeck, J. R., and Long, C. N. H. (1950). *Yale J. Biol. Med.*, **23**, 32.
Green, J. D. (1947). *Anat. Rec.*, **99**, 21.
—— (1948). Ibid., **100**, 273.
—— (1949). *J. Anat., Lond.*, **83**, 82.
—— and Harris, G. W. (1947). *J. Endocrinol.*, **5**, 136.
—— —— (1949). *J. Physiol.*, **108**, 359.
Groot, J. de, and Harris, G. W. (1950). Ibid., **111**, 335.
Harris, G. W. (1944). Thesis for M.D. degree, Cambridge University.
—— (1948a). *Physiol. Rev.*, **28**, 139.
—— (1948b). *J. Physiol.*, **107**, 418.
—— (1950). Ibid., **111**, 347.
—— (1951). *British Medical Journal*, **2**, 559.
—— and Jacobsohn, D. (1951). *Proc. physiol. Soc.* In press.
—— and Johnson, R. T. (1950). *Nature, Lond.*, **165**, 819.
Houssay, B. A., Biasotti, A., and Sammartino, R. (1935). *C.R. Soc. Biol., Paris*, **120**, 725.
Hume, D. M., and Wittenstein, G. J. (1950). *Proc. 1st clin. A.C.T.H. Conf.*, p. 134. John R. Mote, editor. Blakiston Co., Philadelphia, Toronto.
Long, C. N. H. (1947). *Fed. Proc.*, **6**, 461.
—— and Fry, E. G. (1945). *Proc. Soc. exp. Biol., N.Y.*, **59**, 67.
McDermott, W. V., Fry, E. G., Brobeck, J. R., and Long, C. N. H. (1950a). *Yale J. Biol. Med.*, **23**, 52.
—— —— —— —— (1950b). *Proc. Soc. exp. Biol., N.Y.*, **73**, 609.
Markee, J. E., Sawyer, C. H., and Hollinshead, W. H. (1948). *Rec. Progr. Horm. Res.*, **2**, 117.
Masserman, J. H. (1937). *Arch. Neurol. Psychiat., Chicago*, **37**, 617.

Pickford, M., and Vogt, M. (1951). *J. Physiol.*, **112**, 133.
Popa, G. T., and Fielding U. (1930). *J. Anat., Lond.*, **65**, 88.
—— —— (1933). Ibid., **67**, 227.
Richter, C. P. (1933). *Amer. J. Physiol.*, **106**, 80.
Sawyer, C. H., Everett, J. W., and Markee, J. E. (1949). *Endocrinology*, **44**, 218.
—— Markee, J. E., and Townsend, B. F. (1949). Ibid., **44**, 18.
Sayers, G. (1950). *Physiol. Rev.*, **30**, 241.
—— and Sayers, M. A. (1947). *Endocrinology*, **40**, 265.
—— —— (1948). *Rec. Progr. Horm. Res.*, **2**, 81.
Vogt, M. (1944). *J. Physiol.*, **103**, 317.
—— (1951). Ibid. In press.
Westman, A., and Jacobsohn, D. (1938a). *Acta path. microbiol. scand.*, **15**, 301.
—— —— (1938b). *Acta obstet. gynec. scand.*, **18**, 109.
Wislocki, G. B. (1937). *Anat. Rec.*, **69**, 361.
—— (1938). *Res. Publ. Ass. nerv. ment. Dis.*, **17**, 48.
—— and King, L. S. (1936). *Amer. J. Anat.*, **58**, 421.

COMPARATIVE ACTION OF E.C.T. AND OF PITUITARY ANTERIOR LOBE HORMONES ON THYROID FUNCTION

BY

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In a previous paper (Reiss, Hemphill, Maggs, *et al.*, 1951) thyroid function in psychoneurotic and psychotic patients has been evaluated by radioactive tracer technique. The present communication deals with the effects of electric convulsion therapy (E.C.T.) on thyroid compared with that of thyrotrophic, adrenocorticotrophic, and sex hormones.

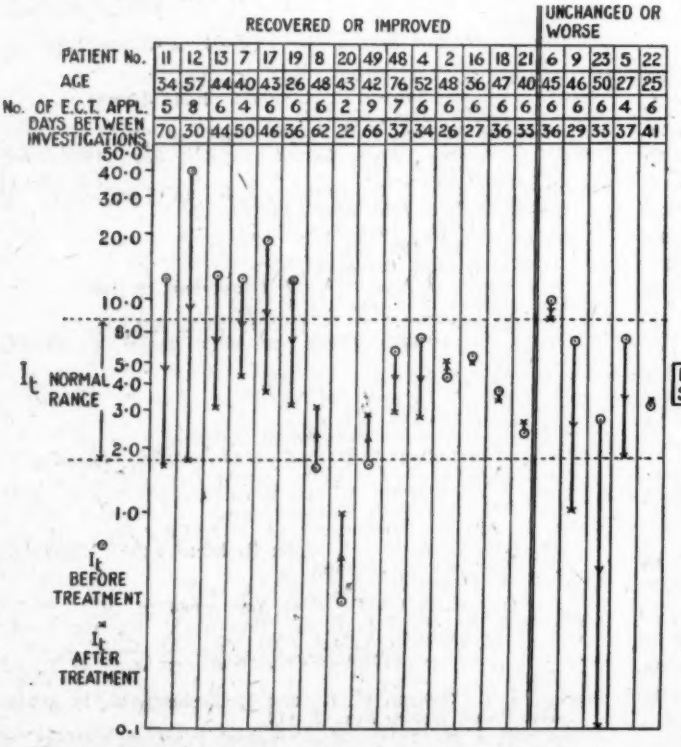

FIG. 1.—Thyroid indices of male patients before and after E.C.T.

Method.—The radioactive tracer method used in all these investigations has been described already (Reiss *et al.*, 1949; Haigh and Reiss, 1950; Reiss *et al.*, 1951). Thyroid function, estimated in this way, is remarkably stable in normal subjects and in untreated stationary psychiatric illness. Table I shows representative results.

TABLE I

Subject No.	Age	Thyroid Investigations		
		First I_t	Interval Between Both Investigations (Days)	Repeat I_t
1	30	14·5	28	16·8
2	33	10·7	21	10·2
3	28	8·0	34	7·4
4	23	6·3	32	6·7
5	28	4·3	356	5·7
6	55	3·3	36	3·4
7	45	0·88	185	0·89
8	30	0·67	354	0·55

In several normal subjects investigated regularly during the past three years thyroid activity did not vary by more than ±10%.

The patients investigated belonged to the usual psychiatric material of out-patient clinics and psychiatric hospitals. However, the majority were cases of depression, normally submitted for E.C.T. In these the expectation of recovery with E.C.T. is high. There were also some other cases, complicated by constitutional and reactive factors, in which the prognosis was uncertain.

Results

Figs. 1 and 2 show the levels of thyroid function in male and female patients before, after completion of, and sometimes during electric shock treatment. The extent and trend of the changes after E.C.T. varied, but were most marked when thyroid function was initially high, which in these cases was always reduced. If the thyroid function was initially subnormal the level rose invariably to normal. Where the level of thyroid function was initially normal it sometimes changed, but only within the normal range. In no case that recovered in which the tracer index had been normal before treatment did the I_t value depart from the normal range with impairment of thyroid function. In some cases the thyroid function did not alter significantly and thus there did not seem to be a ready correlation between the effect of E.C.T. on the thyroid and the therapeutic result. In some cases in which the condition of the patient was unaltered or became worse, occasionally a thyroid function, originally in normal range, became reduced to subnormal; in other similar cases the thyroid function did not alter.

LIMITS OF SIGNIFICANCE

Investigations were made in another series of patients in which only the slope of the iodine uptake was measured, as the urine collection could not be completed. The changes of the slope of uptake K were in agreement with the I_t changes shown in Figs. 1 and 2, and wherever the slope was initially outside normal it was found to be within the normal range after successful E.C.T.

For comparison, Fig. 3 shows changes of thyroid activity after treatment with different hormones in patients suffering from varying psychiatric disorders. The second measurement

was not necessarily made at the same point of development of recovery in all cases. In all the patients treated with thyrotrophic hormone the thyroid function was initially subnormal, but after treatment was within the normal range. Adrenocorticotrophic hormone decreases thyroid activity in different degrees. Its action is thus contrary to that of thyrotrophic hormone. Gonadotrophic hormone of the pituitary anterior lobe was not at our disposal, but treatment with sex hormones, either testosterone and oestrone combined or testosterone or oestrone alone, always reduced thyroid levels.

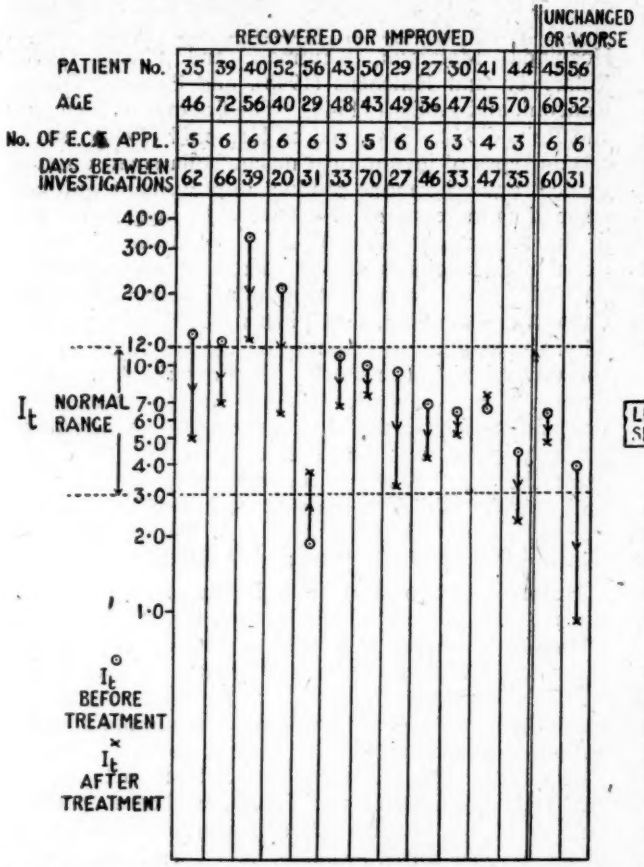
RECOVERED OR IMPROVED
UNCHANGED OR WORSE
PATIENT No. 35 39 40 52 56 43 50 29 27 30 41 44 45 56
AGE 46 72 56 40 29 48 43 49 36 47 45 70 60 52
No. OF E.C.T. APPL. 5 6 6 6 6 3 5 6 6 3 4 3 6 6
DAYS BETWEEN INVESTIGATIONS 62 66 39 20 31 33 70 27 46 33 47 35 60 31
40·0
30·0
20·0
12·0
10·0
NORMAL RANGE
7·0
6·0
5·0
4·0
3·0
2·0
1·0
I_t
I_t BEFORE TREATMENT
I_t AFTER TREATMENT

FIG. 2.—Thyroid indices of female patients before and after E.C.T.

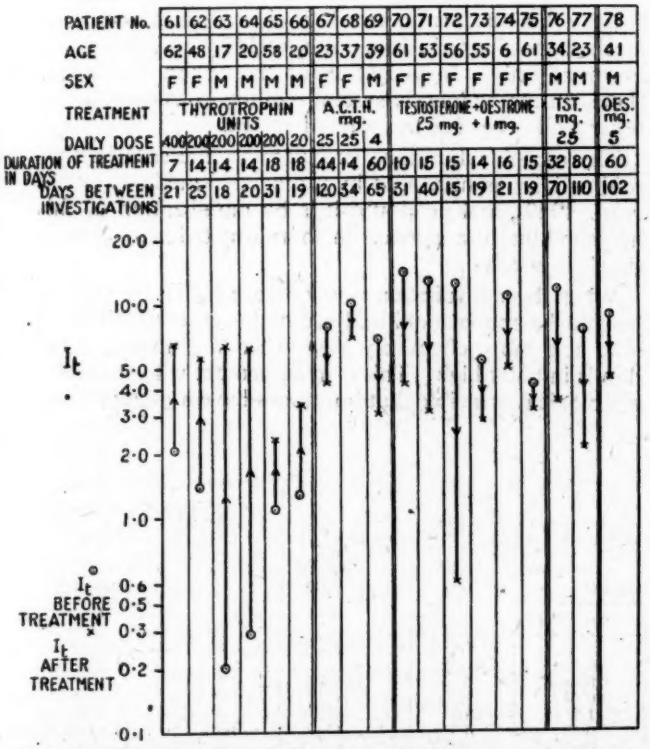

FIG. 3.—Thyroid indices before and after hormone treatment. TST. = Testosterone. OES. = Oestrone.

The results recorded in Fig. 3 show that there is an inverse relationship between the action of thyrotrophic hormone on the thyroid and the action of A.C.T.H. and sex hormones. This fact is confirmed when thyroid function and excretion of steroid hormones during the treatment of patients is studied. Figs. 4 and 5 are examples of such studies which were recently carried out by us on a larger scale (as yet unpublished). Fig. 4 shows that the thyroid activity of a patient suffering from puerperal depression was above normal value, and the 17-ketosteroid and cortin excretion were considerably below normal value. Determination of 17-ketosteroid and cortin excretion was carried out repeatedly. Ten days later, before there had been any change in the psychiatric picture, 17-ketosteroid and cortin excretion began to rise spontaneously. This excretion rate continued to increase, and the patient improved and finally recovered. The thyroid activity was once more assessed, and was now within the normal range.

LIMITS OF SIGNIFICANCE

Similar changes were observed during the stages of recovery of another depressive patient treated with testosterone and oestrone (Fig. 5). In this patient there was a negative adrenal cortex response for ketosteroids, a low 17-ketosteroid excretion in 24 hours, and thyroid hyperactivity. Shortly after the beginning of treatment with testosterone and oestrone the ketosteroid and cortin excretion began to rise and after a month thyroid activity was decreased. There was mental improvement. The adrenal cortex response in ketosteroid excretion was then positive. There seems to be an inverse relationship between the ability of the adrenal cortex to produce 17-ketosteroids in the four hours following stimulation and the response of the thyroid to electric shock.

Table II shows examples. Cases 1, 2, and 3 were unable to mobilize A.C.T.H. endogenously and their adrenals did not respond to A.C.T.H. The thyroid function rose after E.C.T. and they improved. Cases 4 and 5 showed a positive response to A.C.T.H. and glucose; their initially elevated thyroid activity decreased after E.C.T. and they improved mentally. All five patients improved clinically with E.C.T., irrespective of the indications of the adrenal cortex response test. In Case 6 the adrenal cortex responded to A.C.T.H., E.C.T. produced no significant effect on the thyroid, and there was no clinical improvement. In Case 7 the adrenal response to A.C.T.H. was positive; there was no change in thyroid activity after E.C.T. but there was therapeutic improvement.

LIMITS OF SIGNIFICANCE

Discussion

The physiological changes produced by electric shock are complicated, and include circulatory and metabolic changes and alterations in endocrine function. It is by no means certain whether all these changes are beneficial, or in what direction an explanation of the therapeutic effect may be sought. There was perhaps a parallel situation in the early days of endocrinology, when crude hormone extracts were used. The physiological effects

were masked by toxic, anaphylactic, and pyrogenous actions due to impurities in the hormone extract which were not related to the specific biological action desired.

Various authors have studied the action of electric shock treatment by investigating its effects on the endocrine system. Most attention has been directed to the pituitary anterior lobe/adrenal cortical regulatory mechanism only, and the action of E.C.T. on other ductless glands, including the thyroid, has hardly been investigated.

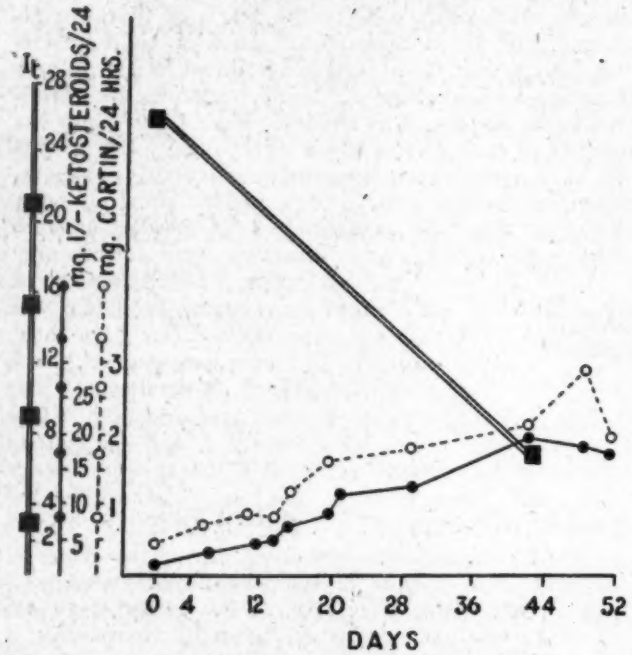

FIG. 4.—Thyroid activity and the excretion of 17-ketosteroid and cortin in a patient suffering from puerperal depression.

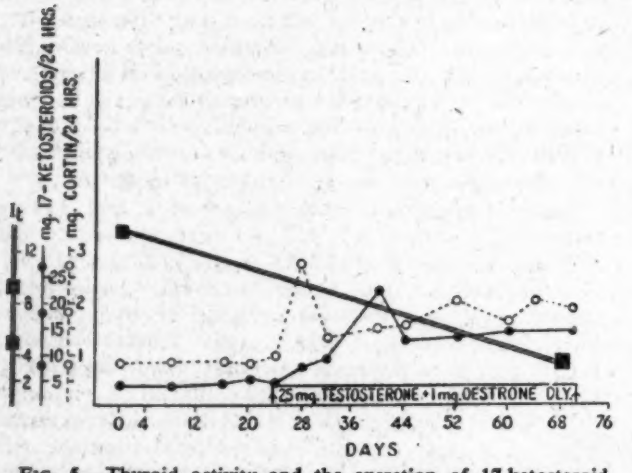

FIG. 5.—Thyroid activity and the excretion of 17-ketosteroid and cortin in a depressive patient treated with testosterone and oestrone.

An increase in the adrenocorticotrophic hormone activity of the pituitary anterior lobe after E.C.T. has been intimated by Hemphill, Macleod, and Reiss (1942), Hoagland, Malamud, Kaufman, and Pincus (1946), Mikkelson and Hutchens (1948), and Parsons, Gildea, Ronzoni, and Hulbert (1949). The findings of Hemphill and Reiss (1942, 1944), and of Hemphill (1946), that in certain types of involutional melancholia small doses of corticotrophic hormone produce improvement with corresponding increases of 17-ketosteroids, suggest that part of the therapeutic effect of shock treatment in involutional melancholia is due to increased mobilization of A.C.T.H. from the anterior pituitary lobe. Hoagland, Callaway, Elmadjian, and Pincus (1950) compared the adrenal activation in response to injected A.C.T.H. and subconvulsive electric shock. They described, in schizophrenic cases, a statistically significant positive correlation and considered that the more responsive the adrenal pituitary system was the better the prognosis for insulin coma therapy. They put forward the proposition that both insulin shock treatment and E.C.T. represent stresses which, when repeated, act therapeutically by releasing endogenously produced A.C.T.H.

However, as shown in Table II, the responsiveness of the pituitary adrenal cortex system is less consistently related to the therapeutic action of E.C.T. than has been assumed. Furthermore, it is by no means certain that A.C.T.H. (measured recently, by ascorbic acid depletion test only) is one uniform hormone or a mixture of different adrenocorticotrophic hormone components. In our patients not only quantitative relations between the A.C.T.H. dose injected and E.C.T., as shown by Hoagland *et al.*, but also considerable qualitative differences in the adrenal cortex response, have been found (awaiting publication). Finally, the treatment with A.C.T.H. of cases that might be expected to respond well to E.C.T. is not often successful, and it is clear that the complex mechanism of E.C.T. does not operate by mobilizing one hormone only. Investigation of the action of electric shock on the endocrine system requires consideration of other glands besides the adrenal cortex.

Thyrotrophic hormone produces an increase in thyroid activity as measured by radioactive methods (Reiss *et al.*, 1949), and no doubt it is by mobilization of this hormone that the increase in thyroid activity by electric shock is effected.

When thyroid function is low before E.C.T., the thyrotrophic hormone mobilized from the anterior pituitary lobe acts more effectively than when the thyroid function is initially high. This is in agreement with the endocrinological principle that hormones have a greater effect

TABLE II

Case No.	Age and Sex	Investigations before E.C.T.					No. of E.C.T. Before Next Investigation	Investigations after E.C.T.	
		Adrenal Cortex Response Tests 17-Ketosteroid Excretion (mg./hr.)				I_t		I_t	Clinical Change
		25 mg. A.C.T.H.		150 g. Glucose					
		Before	After 4 hrs.	Before	After 4 hrs.				
1	52 F	0·82	0·58	0·91	0·40	2·5	5	12·0	Improved
2	56 F	0·34	0·26	0·28	0·20	1·0	4	2·8	"
3	57 F	0·67	0·39	0·58	0·44	7·1	14	9·8	"
4	28 F	—	—	0·60	0·84	12·7	5	3·0	"
5	20 M	0·76	1·2	0·90	1·1	13·3	6	3·3	"
6	60 F	0·17	0·37	0·31	0·22	6·5	4	4·9	Not improved
7	36 F	0·56	0·85	0·45	0·88	5·2	6	5·4	Improved

in underfunction than on normally controlled subjects or in hormone overfunction. Probably when the thyroid function is already above normal range the amount of thyrotrophic hormone mobilized by the action of E.C.T. is not able to increase thyroid function much further, and is perhaps inhibited from doing so by the simultaneous mobilization of A.C.T.H. There appears to be an antagonism between thyrotrophic hormone and A.C.T.H., and A.C.T.H. may inhibit the thyroid. Reiss and Peter (1938) described reduction in blood iodine and atrophy of the thyroid in dogs after treatment with A.C.T.H., and an antagonistic action between thyrotrophic hormone and A.C.T.H. on the blood iodine level. At the same time they noted a decrease in blood iodine in six human cases treated with A.C.T.H., of whom three suffered from Graves's disease. Recent evidence of the antithyrotic action of A.C.T.H. has been reported by R. S. Reiss, Riggs, Thorn, and Forsham (1950).

Probably in many cases E.C.T. operates therapeutically on the anterior lobe/thyroid or anterior lobe/gonadal relationship. It is known that sex hormones in small doses stimulate the anterior pituitary, but large doses inhibit the production of gonadotrophic hormone. The physiological effect of treatment with sex hormones described in this paper may be due to suppression of the production as well as of the function of thyrotrophic hormone by sex hormones acting on the anterior pituitary.

Normal thyroid activity depends on an equilibrium in the production of stimulating and antagonistic hormones. E.C.T. can interfere with the mobilization of pituitary anterior lobe hormones and so influence the total hormone equilibrium. Changes in thyroid activity after E.C.T. are only an indicator for changes in the total hormone equilibrium, irrespective of whether these changes take place inside the normal range only or whether increased or decreased thyroid function is being normalized by E.C.T.

It is not possible at this stage to correlate the therapeutic result of E.C.T. with its physiological effect on one gland. To assume that where the thyroid has been influenced this has been responsible for mental improvement is to imply that a disturbance of thyroid function was originally the cause of the psychiatric illness—an implication not justified without further study. It would be logical to test the supposition by treating psychiatric patients who show a thyroid disturbance from the point of view of this disturbance only. Another way consists in trying to copy the action of the E.C.T. by treating patients with gland concentrates containing all the pituitary anterior lobe hormones.

This is now being attempted in our hospital. Nevertheless, apart from the question of appropriate dosage and the problem of over- and under-sensitivity to hormones, the difficulties are considerable, and deterioration in the progress of the disease and spontaneous remission have to be reckoned with. Our experience shows that thyroid physiology will have to be studied in any further research on the action of E.C.T., and for this the tracer method is convenient and reasonably simple.

Summary

The effect of E.C.T. on thyroid activity has been studied by radioactive tracer technique.

E.C.T. reduces pre-shock hyperactivity and raises pre-shock hypoactivity. Normal pre-shock values are influenced only within the normal range.

This is due to the effect of E.C.T. on the total endocrine equilibrium and especially to the way it influences the antagonism between adrenal cortex and thyroid function.

Relevant problems are discussed and the action of E.C.T. is compared with that of applied hormone therapy.

REFERENCES

Haigh, C. P., and Reiss, M. (1950). *Brit. J. Radiol.*, **23**, 534.
Hemphill, R. E. (1946). *Bristol med.-chir. J.*, **63**, 116.
—— Macleod, L. D., and Reiss, M. (1942). *J. ment. Sci.*, **88**, 554.
—— and Reiss, M. (1942). Ibid., **88**, 559.
—— —— (1944). *British Medical Journal*, **2**, 211.
Hoagland, H., Callaway, E., Elmadjian, F., and Pincus, G. (1950). *Psychosom. Med.*, **12**, 73.
—— Malamud, W., Kaufman, I. C, and Pincus, S. (1946). Ibid., **8**, 246.
Mikkelson, W. P., and Hutchens, T. T. (1948). *Endocrinology*, **42**, 394.
Parsons, E. H., Gildea, E. F., Ronzoni, E., and Hulbert, S. Z. (1949). *Amer. J. Psychiat.*, **105**, 573.
Reiss, M., Haigh, C. P., Hemphill, R. E., Maggs, R., Reiss, J. M., and Smith, S. (1951). *J. Endocrinol.* In press.
—— Hemphill, R. E., Maggs, R., Smith, S., Haigh, C. P., and Reiss, J. M. (1951). *British Medical Journal*, **1**, 1181.
—— —— Murphy, B. M., Halkerston, J. M., and Badrick, R. E. (1949). *J. Endocrinol.*, **6**, 235.
—— and Peter, F. (1938). *Z. ges. exp. Med.*, **104**, 49.
Reiss, R. S., Riggs, D. S., Thorn, G. W., and Forsham, P. H. (1950). *Proceedings of the First Clin. A.C.T.H. Conf.*, Philadelphia, p. 193.

THE ANAEMIA OF RHEUMATIC FEVER

BY

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Anaemia is one of the well-recognized features of rheumatic fever. It is of sudden onset: it may be severe, and it regresses as the acute attack subsides. It is usually classified as an anaemia of secondary type and is described as microcytic or microcytic and hypochromic. Anaemia is a common finding in many acute and chronic infective processes, and the anaemia of acute rheumatism has usually been studied from this aetiological aspect.

Investigations to determine whether it is of haemolytic origin or due to suppression of erythropoiesis have been reported. Douglas and Tannenbaum (1930) consider that infection retards erythropoiesis. In their series, which included three cases of acute rheumatism, they found no evidence of an increase in circulating reticulocytes or of a raised icteric index. Kapp and Coburn (1936) studied the excretion of urinary porphyrin in rheumatic fever and found that the urine of their patients contained abnormally large amounts of coproporphyrin. They state that this does not necessarily indicate increased blood destruction, as it may arise partly or wholly from disturbed liver function. Hubbard and McKee (1939), from a study of recrudescences of rheumatic fever in 17 patients, favour the view that the anaemia is due to suppression of erythropoiesis when the disease is most active, followed by increased red-cell formation as evidenced by a slight but significant increase in reticulocytes as the acute stage regresses. From studies of icteric index, serum bilirubin, and urobilinogen excretion they found little or no evidence of increased blood destruction.

Bradley (1938) introduced an entirely new conception of the problem. He studied a patient with signs of mitral

disease who developed a streptococcal nasopharyngitis and in whom an attack of acute rheumatism was correctly forecast. From haematological data and blood-volume estimations obtained at frequent intervals before and after the onset of the acute attack Bradley concludes that the major part of the apparent anaemia of acute rheumatism results from increased plasma volume, and that the anaemia, as measured by haematocrit or haemoglobinometry, is relative only.

Reid, Watson, and Sproull (1950) have shown that relief of acute rheumatic manifestations is associated first with a fluid shift from intracellular to extracellular fluid compartments, and at this stage the erythrocyte sedimentation rate (E.S.R.) shows no signs of falling. Later, the excess water is removed from the extracellular fluid space mainly by diuresis, and the E.S.R. returns to normal.

In this paper further evidence is presented that the anaemia of acute rheumatism is largely due to haemodilution, and that its severity and relationship to the disease process are governed mainly by fluid shifts within the body.

Methods

Detailed haematological studies were made of 10 patients admitted to hospital with acute rheumatic fever. They were given a standard diet, and the daily fluid intake and urine output were measured. No treatment was prescribed which is known to have a direct effect on erythropoiesis. About every third day at 10 a.m. blood was withdrawn by venepuncture from an elbow vein, using a constant technique. A syringe containing 0.4 ml. of 3.8% sodium citrate was filled to the 2-ml. mark, detached from the needle which remained in the vein, and a small test-tube containing Wintrobe's oxalate mixture was filled to the 5-ml. mark. The citrated sample was used to determine the E.S.R. (Westergren), and haematological data were obtained from the second sample.

Haemoglobin was estimated by the oxyhaemoglobin method of Bell, Chambers, and Waddell (1945), using a photoelectric colorimeter. To test the accuracy of our technique five consecutive readings were made from the same blood sample. The maximum variation was 0.2 g.%. Each patient was allocated a separate haematocrit tube. Red cells were counted, using the same pipette and counting-chamber throughout.

To obtain normal haematological standards for the methods in use blood samples were examined from 16 healthy male and female young adult subjects who had no previous history of blood loss, anaemia, or serious illness. Blood was taken from the female subjects at the intermenstrual phase of the cycle. The same technique was used throughout in subjects and patients.

Results

The values for haemoglobin (Hb), mean corpuscular haemoglobin concentration (M.C.H.C.), and mean corpuscular volume (M.C.V.) in the series of healthy young adult subjects are shown in Table I. In the males the Hb ranged from 12.3 to 14.1 g.%, with a mean value of 13.4 g.%. In the females the corresponding range was 10.3 to 12.8 g.%, with a mean value of 11.9 g.% In the two groups the values for M.C.H.C. and M.C.V. differed only by 0.1% and 1 μ^3 respectively, suggesting that the lower haemoglobin value in the female subject is due to a relatively greater plasma volume compared with total red cells than in the male subject. In the investigations which follow an M.C.H.C. of 29–30% and an M.C.V. of about 80 μ^3 are considered to be within normal limits.

TABLE I.—*Haematological Data in Eight Male and Eight Female Healthy Young Adult Subjects*

Males				Females			
No.	Hb. (g%)	M.C.H.C. (%)	M.C.V. (μ^3)	No.	Hb. (g.%)	M.C.H.C. (%)	M.C.V. (μ^3)
1	13·5	30·7	87	1	11·8	29·6	77
2	14·1	29·7	80	2	12·4	29·7	77
3	12·3	29·3	85	3	12·4	29·5	84
4	14·0	30·4	80	4	11·6	30·4	85
5	13·6	29·6	90	5	11·9	29·8	87
6	13·7	30·0	84	6	12·4	28·8	88
7	12·4	28·2	77	7	12·8	30·5	83
8	13·8	29·7	93	8	10·3	28·6	88
Means	13·4	29·7	85	Means	11·9	29·6	84

Total means: Hb, 12·7 g.%; M.C.H.C., 29·7%; M.C.V., 85μ^3

Haematological data in a series of five male and five female patients at three stages in the course of acute rheumatic fever are shown in Table II. On admission all patients had fever, tachycardia, evidence of active carditis, and acute joint involvement. At this stage the mean Hb value was 9.8 g.%, M.C.H.C. 28.2%, and M.C.V. 86 μ^3. In comparison with the group of normal subjects there is a Hb mean difference of 2.9 g. associated with M.C.H.C. and M.C.V. differences of 1.5% and 1 μ^3 respectively. This would indicate that in the acute stage of rheumatic fever the anaemia is normocytic and normochromic or slightly hypochromic. During the investigation it was noticed that the haemoglobin level often fell further as the acute stage regressed, and this was usually associated with a rise in E.S.R. The blood findings shown under "clinical improvement" in Table II were obtained as soon as there was definite clinical evidence of improvement in the patient's condition. This improvement varied from case to case in detail, but in the main consisted of a fall in temperature, definite relief of arthritis, and obvious subjective improvement. As is shown at this stage, there was a further fall in mean Hb and M.C.H.C. levels of 0.8 g.% and 0.5% respectively, associated with a mean rise in E.S.R. of 7 mm./hr. In the convalescent stage the mean values for M.C.V. and M.C.H.C. showed very little change from those in the acute stage, though the mean Hb value had risen by 1.8 g.%.

TABLE II.—*Haematological Data in Ten Patients at Three Stages in the Course of Acute Rheumatic Fever*

		Acutely Ill				Clinical Improvement				Convalescent			
No.	Sex	Hb (g.%)	M.C.H.C. (%)	M.C.V. (μ^3)	E.S.R. (mm./hr.)	Hb	M.C.H.C.	M.C.V.	E.S.R.	Hb	M.C.H.C.	M.C.V.	E.S.R.
1	F	8·5	26·6	86	85	8·4	27·1	98	85	11·6	27·8	88	10
2	F	9·7	28·2	79	90	9·0	27·3	86	105	12·4	29·5	87	6
3	F	9·5	31·0	86	124	9·7	30·3	—	105	12·0	30·0	81	8
4	F	11·3	29·7	87	111	9·2	28·6	77	101	11·1	28·3	—	45
5	F	8·5	27·4	90	95	7·7	26·6	—	125	11·6	28·3	85	10
6	M	9·1	27·6	84	100	8·1	26·1	—	92	11·6	27·9	83	8
7	M	10·0	29·0	90	104	9·5	28·8	—	123	11·1	28·8	78	7
8	M	9·8	28·0	90	121	8·8	26·7	—	128	10·9	26·6	73	21
9	M	9·6	27·0	80	60	9·0	28·0	78	54	11·4	27·0	87	16
10	M	12·1	27·5	80	71	9·9	27·5	93	106	12·5	28·4	86	20
Means		9·8	28·2	86	96	9·0	27·7	—	103	11·6	28·3	83	15

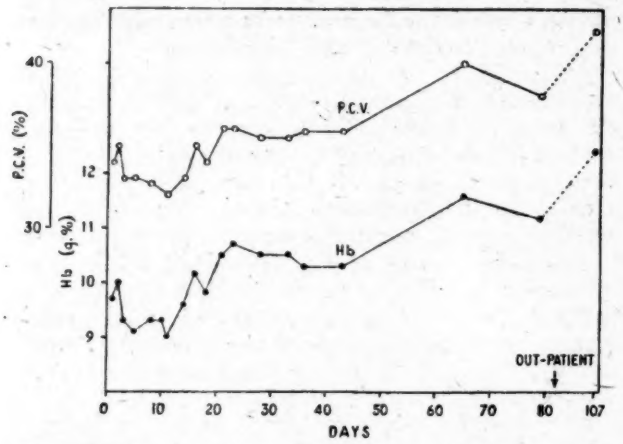

FIG. 1.—The close direct relationship of haemoglobin and packed cell volume in a patient during the course of acute rheumatic fever.

In all cases haemoglobin levels and haematocrit values ran parallel both in the development and in the regression of the anaemia. In about 200 observations there was practically no instance in which a fall or rise in Hb of at least 0.2 g.% was unaccompanied by a corresponding fall or rise in packed red cell volume (P.C.V.), which was not always equivalent and which accounted for the minor changes in M.C.H.C. that occurred. The close direct relationship of Hb and P.C.V. throughout the course of rheumatic fever is shown in Fig. 1.

The results so far can be interpreted as indicating haemodilution in the acute stage of rheumatic fever. A fluid shift from intracellular to extracellular compartments is consistent with the observed fall in haemoglobin level which occurs as the acute stage of the disease regresses. Further support for this hypothesis is given by the rapidity of development of the anaemia. This was very noticeable when blood examination was done at intervals of two to three days. Falls in haemoglobin concentration of 1 g.% during a three-days interval occurred commonly. Usually such a fall was accompanied by a reduction in M.C.H.C. of 0.5–1%. One patient who had made a good recovery and whose blood findings had returned to normal levels relapsed while in hospital. A fall in Hb of 1.7 g.% in two days was observed. This was accompanied by an equivalent fall in P.C.V., and the M.C.H.C. showed a reduction of only 0.4%. The blood data and the changes in E.S.R. in this patient are shown in Fig. 2. A rise in E.S.R. is accompanied by a fall in Hb and P.C.V., and later, as the E.S.R. returns to normal, there is a rise in Hb and P.C.V.

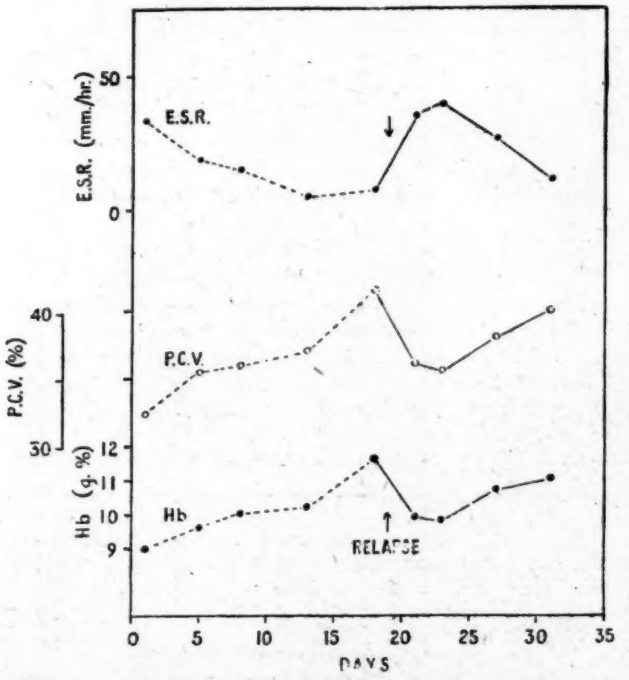

FIG. 2.—The changes in haemoglobin, packed cell volume, and E.S.R. in a patient who had a relapse of acute rheumatic fever.

As a further test of haemodilution, fluid-balance studies were carried out on each patient. Daily fluid intake and urine output were carefully measured and the totals subtracted. No account was taken of fluid lost by sweating, respiration, or in the faeces, owing to the technical difficulties of such a complete balance study. Marked sweating in rheumatic fever occurs as the temperature is subsiding, and would affect the fluid balance to any great extent only during the first two to three days of observation. As an example of the changes observed, the fluid balance chart is plotted with haemoglobin and E.S.R. levels in one patient throughout an attack of acute rheumatic fever (Fig. 3). There is an

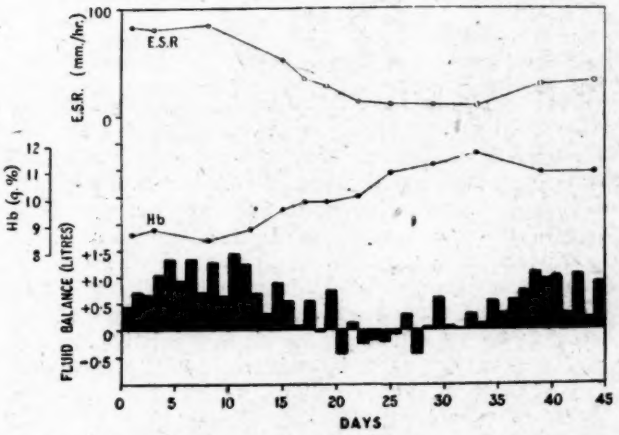

FIG. 3.—The relationship of fluid balance, haemoglobin, and E.S.R. in a patient throughout the course of acute rheumatic fever.

inverse relationship between the haemoglobin and E.S.R. curves, and a rise in haemoglobin is associated with a relative increase in fluid output over intake. Fig. 3 shows definite negative fluid balance over a period of five to eight days while the haemoglobin level is rising steeply. As no account is taken of fluid lost by other channels than urine it is assumed that, in this patient, fluid previously retained in excess by the body is being excreted. The inverse relationship between haemoglobin and E.S.R. was very striking in all patients studied, and the haemoglobin level at any one point in the illness served as a good indication of rheumatic activity.

In one patient frequent plasma-volume determinations (Gregersen and Stewart, 1939) were made throughout the course of an attack of rheumatic fever. The results were plotted against haemoglobin levels obtained just before each volume estimation (Fig. 4). The curves for haemoglobin and plasma volume showed an inverse relationship, indicating that variations in haemoglobin level were due to variations in plasma volume.

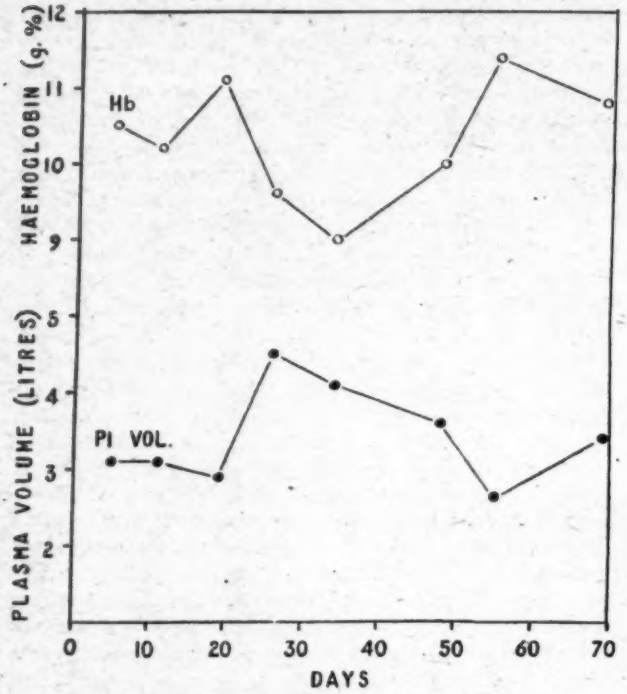

FIG. 4.—The inverse relationship of haemoglobin and plasma volume in a patient throughout the course of rheumatic fever.

Discussion

Previous reports have failed to show any evidence of a haemolytic process in acute rheumatism. In this investigation no special studies were made to detect haemolysis, but no patient ever showed clinical evidence of icterus, and the blood plasma remained pale and watery during the rapid falls in haemoglobin level described and throughout the course of the disease. From a consideration of the haemoglobin, haematocrit, and red-cell measurements obtained, the anaemia can be explained by one of two processes: (*a*) a relative increase in plasma volume—that is, hydraemia—or (*b*) a supression of erythropoiesis resulting in a relative reduction in red-cell mass without any change in total blood volume. The speed of development of the anaemia weighs against the latter possibility; also a raised blood volume in rheumatic fever has been observed in this and in other investigations, and it would seem that the anaemia is largely due to a relative increase in plasma volume without coincident increase in red-cell mass. The anaemia is normocytic and normochromic or slightly hypochromic.

The blood findings throughout the illness support the view that cure of acute rheumatism is associated, first, with a fluid shift from the intracellular to the extracellular fluid compartments, followed by a reduction in the latter by diuresis. It has been shown that the haemoglobin level reaches a lower value after clinical signs of improvement have occurred, and this is compatible with the fluid shift described. Later, as the haemoglobin level returns to normal, fluid-balance studies indicate that this is associated with a relative increase in urine output compared with fluid intake. At the same time the E.S.R. returns to normal.

The ease of obtaining a blood sample by venepuncture in the acute stage of rheumatic fever compared with the convalescent stage is perhaps further evidence of increased blood volume. In the acute stage the blood usually spurts from the needle, compared with the slow drip in late convalescence.

An increase in reticulocyte level, small but significant, has been shown to occur in rheumatic fever shortly after the stage of greatest disease activity (Hubbard and McKee, 1939). This may be caused by the stimulus of relative anoxia due to a further increase in plasma volume rather than be the result of release of the bone marrow from the influence of a metabolic or other toxin.

The minor changes in M.C.H.C. which occurred are considered to be real, but further investigation is required. Changes in the osmotic pressure of the plasma may cause variations in red-cell size with resultant alterations in M.C.H.C. The latter showed a tendency to fall and rise with the haemoglobin level. While the haemoglobin level falls there is haemodilution and reversal of the albumin/globulin ratio, and both these factors would tend to reduce osmotic pressure, increase red-cell size, and lower M.C.H.C. The reverse would occur as the disease regresses. The reticulocyte increase described above may also play a part in the small reduction of the M.C.H.C. in the early stages of the illness. As estimation of mean cell volume depends on the relatively inaccurate red-cell count, it is intended to carry out direct osmotic pressure measurements to test this theory.

The role of hydraemia and changes in the osmotic pressure of the plasma in anaemia have in the past perhaps not received adequate consideration. Further investigation of these factors may prove of value, especially in anaemias associated with infection. The anaemia of rheumatic fever in particular may have a complete explanation in quantitative and qualitative alterations in the plasma as opposed to functional derangement of the red bone marrow.

Summary

The anaemia of rheumatic fever has been investigated by a detailed haematological study of 10 patients.

Evidence is presented that the anaemia is normocytic and normochromic or slightly hypochromic, and is largely due to hydraemia without alteration in total cell mass.

The anaemia is related to fluid shifts occurring during the rheumatic attack.

It is suggested that hydraemia and changes in the osmotic pressure of the plasma may be important factors in this and other anaemias associated with infection.

I thank Professor J. W. McNee and Dr. James Reid for advice, interest, and encouragement throughout the investigation.

REFERENCES

Bell, G. H., Chambers, J. W., and Waddell, M. B. R. (1945). *Biochem. J.*, **39**, 60.
Bradley, W. H. (1938). *Proc. int. Congr. Rheum.*, p. 86. London.
Douglas, A. H., and Tannenbaum, H. (1930). *Arch. intern. Med.*, **45**, 248.
Gregersen, M. I., and Stewart, J. D. (1939). *Amer. J. Physiol.*, **125**, 142.
Hubbard, J. P., and McKee, M. H. (1939). *J. Pediat.*, **14**, 66.
Kapp, E. M., and Coburn, A. F. (1936). *Brit. J. exp. Path.*, **17**, 255.
Reid, J., Watson, R. D., and Sproull, D. H. (1950). *Quart. J. Med.*, **19**, 1.

According to the *Manchester Guardian* (August 22) Mr. R. S. McLaughlin, a Canadian businessman, has given over $1,000,000 to start a medical foundation which will be for the most part devoted to fellowships enabling their holders to maintain a family if they are living abroad; it will also be used to support clinical and medical research in Canada. Dr. W. E. Gallie, formerly Professor of Surgery and Dean of the medical school at Toronto, is one of the three trustees.

INCIDENCE OF CONGENITAL MALFORMATIONS AND THEIR RELATION TO VIRUS INFECTIONS DURING PREGNANCY

BY

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Evidence is accumulating about the aetiology of congenital malformations. Reviewing this evidence, Warkany (1947) mentioned genetic, nutritional, chemical, endocrine, actinic, infectious, and mechanical factors, each of these having been recognized either from clinical observations or from animal experiments as of some causal significance. Similar reviews have been made in this country by Landtman (1948), Penrose (1951), and Carter (1951). This increasing knowledge about the causes of congenital malformations is bringing nearer the day when effective preventive action will be possible and when these malformations will cease to be the unexplainable and unavoidable misfortunes that they have been in the past.

The purpose of this paper is to review what is already known about the incidence of congenital malformations from the statistical aspect and to summarize the results of some of the investigations that have been made in various parts of the world into the effects of virus infections during pregnancy.

Information about the incidence of congenital malformations is available from national mortality statistics, Scottish stillbirth statistics, and from special studies of limited series of cases.

Mortality Statistics

During the three years 1946–8 16,324 deaths at all ages registered in England and Wales (Registrar General) were attributed to congenital malformations, and three-quarters of these were of infants under 1 year of age (Table I). Congenital malformations ranked third among the causes of infant mortality, preceded by prematurity and pneumonia. They caused 12% of all infant deaths, 14% of deaths under 4 weeks, and 11% of deaths between 4 weeks and 1 year. Of the total of 16,324 deaths 10% were of infants in their first day of life, 36% between 1 day and 4 weeks, 28% between 4 weeks and 1 year, 10% between 1 and 15 years, and 16% at higher ages.

TABLE I.—*Deaths from Congenital Malformations in England and Wales by Sex and Age, 1946–8*

A. Under 1 Year

	Under 1 Day	1–6 Days	7–13 Days	14–20 Days	21–27 Days	4 Wks–3 Mths	3–6 Mths	6–9 Mths	9–12 Mths
Males	863	1,712	745	404	330	1,542	721	303	157
Females	781	1,372	702	375	247	893	586	274	142
Persons	1,644	3,084	1,447	779	577	2,435	1,307	577	299

B. All Ages (Years)

	0–	1–	2–	3–	4–	5–	10–	15 and Over	All Ages
Males	6,777	281	128	63	49	182	134	1,371	8,985
Females	5,372	242	88	54	52	126	120	1,285	7,339
Persons	12,149	523	216	117	101	308	254	2,656	16,324

The infant mortality rate from congenital malformations was about 6 per 1,000 live births between 1931 and 1939, increased to over 6.5 during 1940 to 1942, but has since declined by about one-third to 4.45 per 1,000 in 1948 (Table II). This decline is identical with that of total infant mortality during the same period—namely, from 51 per 1,000 in 1942 to 34 in 1948. As there is no reason to believe that the *incidence* of these malformations can have substantially diminished in the last few years, the reduction in mortality means that a larger proportion of children born with malformations have been saved from dying in infancy.

TABLE II.—*Infant Mortality Rates from Congenital Malformations per 1,000 Related Live Births. England and Wales, 1931–48*

1931	5·66	1937	6·28	1943	5·89
1932	6·03	1938	6·22	1944	5·52
1933	5·98	1939	6·09	1945	5·60
1934	6·32	1940	6·62	1946	5·43
1935	6·12	1941	6·56	1947	4·88
1936	6·36	1942	6·50	1948	4·45

During 1946–8 the neonatal mortality rate from congenital malformations was highest in the North IV region of England and Wales (Cheshire and Lancashire), where the rate was 20% above the national average, and lowest in Greater London, the East and South-east regions (Table III). These, it should be noted, were

TABLE III.—*Infant Mortality Rates from Congenital Malformations at Ages Under 4 Weeks and from 4 Weeks to 1 Year by Geographical Regions, Percentage of Rate for England and Wales, and Percentage of Infant Mortality from all Causes. Average of Rates in 1946, 1947, and 1948*

	Under 4 Weeks			4 Weeks–1 Year			Total Under 1 Year		
	Deaths from Congenital Malformation per 1,000 Related Live Births	% E. & W.	% of Infant Mortality from all Causes	Deaths from Congenital Malformation per 1,000 Related Live Births	% E. & W.	% of Infant Mortality from all Causes	Deaths from Congenital Malformation per 1,000 Related Live Births	% E. & W.	% of Infant Mortality from all Causes
England and Wales	3·04	100	14	1·88	100	11	4·92	100	12
South-east	2·77	91	15	1·66	88	13	4·43	90	14
Greater London	2·74	90	15	1·70	90	13	4·44	90	14
Remainder of South-east	2·80	92	14	1·63	87	14	4·43	90	14
North	3·29	108	13	2·10	112	9	5·39	110	11
North I	2·95	97	12	2·00	106	8	4·95	101	10
" II	3·08	101	13	1·71	91	9	4·79	97	11
" III	2·96	97	13	2·07	110	11	5·03	102	12
" IV	3·64	120	14	2·24	119	9	5·88	120	12
Midland	3·19	105	14	1·86	99	11	5·05	103	12
Midland I	3·18	105	14	1·82	97	10	5·00	102	12
" II	3·23	106	14	1·92	102	11	5·15	105	12
East	2·77	91	14	1·70	90	13	4·47	91	13
South-west	3·12	103	14	1·74	93	15	4·86	99	14
Wales	2·89	95	12	2·41	128	12	5·30	108	12
Wales I	2·80	92	11	2·44	130	11	5·24	107	11
" II	3·13	103	13	2·26	120	12	5·39	110	13

TABLE IV.—*Deaths from Congenital Malformations at all Ages, occurring in Each Month; and, with Correction for Varying Length of Months, Percentage of Average Monthly Deaths. England and Wales, 1946–8*

	Total	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.-Mar. and Oct.-Dec.	April-Sept.
All congenital malformations	16,313	1,550	1,413	1,541	1,395	1,426	1,244	1,233	1,180	1,236	1,300	1,314	1,481	8,599	7,714
	100	*112*	*112*	*111*	*104*	*103*	*93*	*89*	*85*	*92*	*94*	*98*	*107*	*106*	*94*
Congenital hydrocephalus	890	78	89	92	62	82	63	77	56	76	68	76	71	474	416
	100	*103*	*129*	*122*	*85*	*109*	*86*	*102*	*74*	*104*	*90*	*104*	*94*	*107*	*93*
Spina bifida and meningocele	3,150	292	248	249	278	295	259	271	247	243	252	243	273	1,557	1,593
	100	*109*	*101*	*93*	*108*	*110*	*100*	*101*	*92*	*94*	*94*	*94*	*102*	*99*	*101*
Congenital malformation of heart	5,247	526	490	511	427	449	375	373	352	411	392	436	505	2,860	2,387
	100	*118*	*120*	*115*	*99*	*101*	*87*	*84*	*79*	*95*	*88*	*101*	*113*	*109*	*91*
Monstrosities	311	27	25	29	30	31	22	20	30	22	32	22	21	156	155
	100	*102*	*104*	*110*	*117*	*117*	*86*	*76*	*114*	*86*	*121*	*86*	*80*	*101*	*99*
Congenital pyloric stenosis	825	98	90	93	88	68	66	64	47	44	53	53	61	448	377
	100	*140*	*141*	*133*	*130*	*97*	*97*	*91*	*67*	*65*	*76*	*78*	*87*	*109*	*91*
Cleft palate, hare-lip	231	19	21	18	15	21	27	12	26	13	20	17	22	117	114
	100	*97*	*117*	*92*	*79*	*107*	*142*	*61*	*133*	*69*	*102*	*90*	*112*	*102*	*99*
Imperforate anus	143	21	9	10	16	9	14	17	6	8	11	7	15	73	70
	100	*173*	*81*	*82*	*136*	*74*	*119*	*140*	*49*	*68*	*91*	*60*	*124*	*102*	*98*
Cystic disease of kidney	671	53	58	64	61	62	66	51	58	49	46	45	58	324	347
	100	*93*	*111*	*112*	*111*	*109*	*120*	*90*	*102*	*89*	*81*	*82*	*102*	*97*	*103*
Other stated and unstated malformations*	4,845	436	383	475	418	409	352	348	358	370	426	415	455	2,590	2,255
	100	*106*	*102*	*115*	*105*	*99*	*88*	*85*	*87*	*93*	*104*	*104*	*111*	*107*	*93*

* Malformations of central nervous system 9%, of circulatory system 21%, of digestive system 44%, of genito-urinary system 9%, other 13%, unstated 4%.
NOTE: The difference in total deaths shown in Tables I and IV arises because Table I gives deaths registered, and Table IV gives deaths occurring in the periods concerned.

the regions reporting the highest and the lowest rates of neonatal mortality from all causes. The regional differences do not therefore provide definite evidence of variability in the incidence of congenital malformations in different parts of the country.

Adjustment being made for different length of months, most deaths from congenital malformations at all ages occurred in January, February, and March, and fewest in August (Table IV). Largest variations between winter and summer deaths were from congenital malformations of the heart, pyloric stenosis, hydrocephalus, and from the group of "other stated and unstated malformations."

Table V, which gives the percentage distribution of deaths at different ages by type of malformation, shows that, in infancy and childhood, mortality was greatest from malformations of the heart, but that amongst adults this group was surpassed by "other stated malformations."

TABLE V.—*Percentage Distribution of Deaths from Congenital Malformations at Various Ages by Type of Malformation. England and Wales, 1946–8*

	Under 1 Year	1–4 Years	5–14 Years	15 Years and Over	All Ages
All congenital malformations	100	100	100	100	100
Congenital hydrocephalus	5	16	10	3	5
Spina bifida, meningocele	25	10	3	1	19
Congenital malformation of heart	32	38	50	23	33
Monstrosities	3	0	—	—	2
Congenital pyloric stenosis	7	1	—	0	5
Cleft palate, hare-lip	2	3	0	—	1
Imperforate anus	1	0	0	—	1
Cystic disease of kidney	1	1	2	22	4
Other stated malformations	22	31	35	51	29
Unstated malformation	2	0	0	0	1

At all ages, deaths of males from malformations of all types exceeded deaths of females by 22%—a 26% excess of males in infancy, a 23% excess at 1–14, and a 7% excess at adult ages (Table VI). Most of the specified types of congenital malformations showed excess of male mortality, especially pyloric stenosis, but notable exceptions were spina bifida and meningocele, and monstrosities from which there were more deaths of female children than of male. Congenital malformations of the heart caused more male than female deaths in infancy and adult life but not during the years of childhood.

TABLE VI.—*Deaths of Males from Congenital Malformations as Percentage of Deaths of Females, by Age and Type of Malformation; England and Wales, 1946–8*

	Under 1 Year	1–14 Years	15 Years and Over
All congenital malformations	126	123	107
Congenital hydrocephalus	115	169	157
Spina bifida, meningocele	70	56	153
Congenital malformation of heart	142	94	114
Monstrosities	88	—	—
Congenital pyloric stenosis	396	—	—
Cleft palate, hare-lip	113	81	—
Imperforate anus	286	300	—
Cystic disease of kidney	335	300	91
Other stated malformations	154	176	107
Unstated malformation	106	100	—

Stillbirth Statistics

Since 1939 provision has been made in Scotland for the reporting of causes of stillbirth. During 1945–7, 9,995 stillbirths were registered, of which 1,706 were ascribed to congenital malformations (Registrar General for Scotland). This yields congenital malformation rates of 17.1% of all stillbirths and 5.42 per 1,000 total births, live and still.

Of the 1,706 stillbirths attributed to congenital malformations 44% were from anencephaly, 30% from hydrocephalus, 8% from spina bifida, 9% from multiple malformations, 1% from heart disease, and 8% from other stated or unstated malformations.

Special Studies of Stillbirth and Infant Deaths

In Birmingham, McKeown, Record, and MacMahon have studied consecutive cases of congenital malformations resulting in stillbirth or death in infancy during 1940–7. McKeown (unpublished data) gave the following rates per 1,000 births, live and still: anencephaly 2.3, spina bifida 2.5, hydrocephalus 0.9, other malformations of the central nervous system 0.2, congenital malformations of the heart 1.8, pyloric stenosis 0.3, mongolism 0.2, hare-lip, cleft-plate 0.2, other malformations 1.6. Altogether these yielded a total rate of stillbirths and infant deaths from congenital malformations of 10 per 1,000 births. The corresponding combined rate in Scotland in 1945 was 11.4.

Murphy (1947) examined the certified causes of stillbirths and deaths at all ages in Philadelphia during 1929–33 and estimated that there had been 47 deaths or stillbirths associated with congenital malformations per

10,000 live births during the period, or 1 to 213. Unfortunately, disregarding the fact that he was dealing only with deceased or stillborn cases, he summed up his findings as, "One malformed child was born for every 213 infants who were born alive." He used this ratio as if it measured the total incidence of congenital malformations, and this drew from Carter and Tizard (1951) the comment that this ratio of 1 in 213 was "much too low on any definition of congenital defect."

Murphy's series included 222 stillbirths from congenital malformations out of a total of 7,478 stillbirths, or 3%, a much smaller proportion than the 17.1% reported in Scotland in 1945–7.

Estimates of Total Incidence

Each of the foregoing sources has provided information about the incidence of malformations where stillbirth or death had resulted, but not about the total incidence of malformations, fatal and non-fatal. A few investigators have estimated the total incidence of malformations among series of births. They have usually dealt, however, with births in hospital, and these are perhaps not representative of births in general. Some of the difficulties in making estimates of this kind were discussed in a recent "Any Questions?" paragraph in the *British Medical Journal* (1950), and "1 in 40" was given as a reasonable estimate of the chance that any random pregnancy would end in a serious malformation.

Malpas (1937) reported on 13,964 births in the Liverpool Maternity Hospital; among these he found 294 cases of congenital malformation, or 2.1%. Of these, 149, just over 50%, were malformations of the central nervous system.

Naujoks (1938), in Cologne, found 236 malformed children (1.33%) in a series of 17,800 births. These 236 cases included 28 with hydrocephalus, 7 with anencephaly, 6 with hydrops foetalis, 15 with spina bifida or meningocele, 29 with hare-lip, cleft palate, 7 with other cranial malformations, 11 with malformations of upper limbs, 60 with malformations of lower limbs, 24 with polydactyly or syndactyly, and 39 with rare minor defects.

Javert and Stander (1943) reported that 2.95% of 27,000 infants delivered in their clinic had some abnormality, including extra digits, birth marks, undescended testicle, umbilical hernia, spina bifida, and hydrocephalus.

Tholen (1946), in Holland, found 66 children with congenital malformations out of 1,833 born during 1944–6, or 3.6%. The malformations were as follows: anencephaly 5, hydrocephalus 4, macerated foetus 18, pes valgus 1, pes varus 3, spina bifida 6, gastro-intestinal atresia 2, imperforate anus 3, hypospadias 1, epispadias 1, mongolism 6, cephalocele 1, malformation of heart 7, malformation of toes or fingers 5, congenital retro-auricular fistula 1, bilateral congenital cataract 2.

Landtman (1948) found 73 malformed children (2.0%) among 3,593 deliveries during 1945–8 at University College Hospital, London. The malformations were: anencephaly 12, spina bifida 6, hare-lip, cleft palate 5, mongolism 4, deformities of limbs 13, congenital heart disease 11, hypospadias 4, miscellaneous 18.

Greenberg *et al.* (1949), in a paper to which further reference is made below, found 30 children with congenital defects (1.37%) in a control series of 2,186 deliveries of women who had not been vaccinated against smallpox during pregnancy.

The percentages of malformed children found in these six separate series were therefore 2.1, 1.33, 2.95, 3.6, 2.0, and 1.37, giving an average 2.23. The average of these heterogeneous sets of data is of doubtful value. Nevertheless, it corresponds quite well with the estimate of 1 in 40 (2.5%) quoted by the *British Medical Journal* and based partly on the same evidence. Either may be taken as a rough indication of the total incidence of congenital malformations, or, at any rate, of those conditions that are generally recognized as such in investigations into their incidence. Clearly, however, the actual incidence found in any investigation will depend upon how widely or narrowly congenital malformations are defined for the purpose of that investigation.

Some further details about the incidence of congenital malformations, with additional references, are given in the Ministry of Health Report No. 94 (1949) on neonatal mortality and morbidity.

Influence of Virus Infections during Pregnancy

Swan (1949) has reviewed much of the work that has been done by himself and others in the investigation of the association between maternal rubella and congenital malformations, stillbirths, and abortions, an association to which attention was first drawn by Gregg (1941). Practically all of the early evidence adduced in support of this association was based on *retrospective* inquiries. Starting with the recognition of congenital malformation in the child, inquiry was made into the mother's health during pregnancy, and in a high proportion of cases a history of rubella in pregnancy was elicited. Moreover, the attack of rubella had usually occurred at some time during the first three months of pregnancy—a most important finding, as it strongly suggested that factors other than chance were involved. The double event of congenital malformation preceded by rubella early in pregnancy was found so often that there seemed little room for reasonable doubt about the existence of a causal relationship; and, as a result of inquiries of this retrospective type, it was estimated that, following an attack of rubella during the first two months of pregnancy, the chances of the child being malformed were not far short of 100% (Swan *et al.*, 1943).

It is important to realize that inquiries of this retrospective type are apt to give a misleading estimate of the degree of risk of congenital malformation following maternal rubella—first, because the cases of congenital malformation have already been selected before inquiry about the pregnancy is made; and, secondly, because the mother's recollection of events early in pregnancy may be faulty or may be influenced by the fact that she has given birth to a malformed child. It may be, therefore, that the actual risk has been greatly exaggerated. Some clinicians have adopted the policy of advising induction of abortion when rubella has occurred early in pregnancy, in the belief that otherwise the birth of a malformed child is almost certain. Before advocating such a drastic procedure as termination of pregnancy, however, they should understand that the *statistical evidence as yet available*, pointing to an almost 100% probability of malformation, is of a dubious and unsatisfactory character.

Retrospective inquiries from the abnormal child to the mother answer only the question (and, as has already been implied, do not necessarily answer it well)—"What is the probability that the mother of a malformed child had rubella during pregnancy?" The question, or rather double question, that has to be answered is: "What is the probability that rubella during pregnancy will result in the birth of a malformed child, and how does the incidence of congenital malformations following maternal rubella compare with the incidence of congenital malformations among newborn children in general?"

An answer to this double question can be obtained satisfactorily only from a *prospective* inquiry that takes the mother's health during pregnancy as the starting-point and proceeds forward from there to consider the condition of the child. This has been fully realized by a number of investigators, and results of several inquiries framed on those lines are already on record. Unfortunately, as there are considerable practical difficulties to be overcome in carrying out a satisfactory *prospective* inquiry, the results so far reported tend to be conflicting and confusing. In a number of inquiries the possible effects of diseases other than rubella have also been investigated.

Prospective Inquiries Reported in the Literature

Fox and Bortin (1946) investigated the outcome of 11 cases of maternal rubella (9 in the first three months of pregnancy) ascertained from Milwaukee Public Health Department records. One child was hydrocephalic and stillborn. Another was described as a "blue baby" with hydrocephalus; it survived, and was reported as having become normal. In each of these two cases rubella had occurred during the first three months of pregnancy. No abnormality was noted in the 10 other children (one set of twins).

Aycock and Ingalls (1946) used the Board of Health records of two Massachusetts communities to discover four cases of maternal rubella. Two had occurred in the first three months of pregnancy, and one of the resulting children was mentally retarded; the other was normal, as were the two children from the other two cases. The same authors also followed up 131 cases of poliomyelitis during pregnancy (27 in the first three months)—92 of the children born were normal; 33 pregnancies ended in abortion or stillbirth (13 where poliomyelitis had occurred during the first three months of pregnancy); three children had poliomyelitis; another child was "lame"; and two had congenital malformations. In both of these last two cases the attack of poliomyelitis had been in the first three months of pregnancy.

Ober, Horton, and Feemster (1947) sent out postal inquiries to some 3,000 Massachusetts women, aged 17–49, reported as having had rubella in 1943. Only 41% of the women replied to the inquiry, and 49 of them said they had been pregnant at the time when the attack of rubella had taken place. Five more cases were introduced into the inquiry by "supplementary methods." In 22 out of these 54 cases rubella had occurred during the first three months of pregnancy. These 22 cases resulted in 5 children born with congenital defects and 6 pregnancies terminating in stillbirth or abortion. The other 32 cases in which rubella had occurred after the third month of pregnancy produced 3 defective children and 3 abortions or stillbirths.

Grönvall and Selander (1948) reported from Sweden on the outcome of pregnancies complicated by a variety of infectious diseases. Their results can most conveniently be presented in tabular form (Table VII).

TABLE VII.—*Summary of the Results Published by Grönvall and Selander (1948)*

Type of Infectious Disease	Infection Occurring During First 3 Months of Pregnancy				Infection Occurring After First 3 Months of Pregnancy			
	Total No. of Children	Aborted or Stillborn	Live-born but with Malformation	Normal	Total No. of Children	Aborted or Stillborn	Live-born but with Malformation	Normal
Rubella ..	13	2	—	11	15	1	1	13
Measles ..	4	2	—	2	16	1	—	15
Varicella ..	4	—	—	4	9	1	—	8
Mumps ..	6	1	1	4	28	—	4	24
Acute hepatitis ..	10	1	1	8	19	3	—	16
Poliomyelitis ..	15	7	1	7	23	4	1	18
Scarlet fever ..	3	—	—	3	10	—	—	10
Herpes zoster ..	2	1	—	1	—	—	—	—

Fox, Krumbiegel, and Teresi (1948) investigated 6 cases of maternal measles (1 in the first three months of pregnancy), 23 cases of mumps (6 in the first three months), and 4 cases of chicken-pox (1 in the first three months). Only one child had a congenital malformation—hare-lip following maternal measles in the fourth month of pregnancy. A control series was also studied consisting of 665 children born to 297 women who had had one of these three infectious diseases in 1942–5 before or after but not during pregnancy. Six cases of congenital malformations were discovered in the control series.

Through the medium of a syndicated health column, Abel and Van Dellen (1949) invited readers who had had an attack of rubella during pregnancy to write and tell them about the outcome relative to the child. They received details of 82 pregnancies, resulting in the birth of 84 children. Of 54 children born to women whose attack of rubella had been in the first trimester of pregnancy, 3 were stillborn, 44 had congenital malformations, and 7 were normal. Of the other 30 children 12 had malformations and 18 were normal. The authors themselves drew attention to the obvious imperfections of their method of inquiry, but surprisingly suggested that, because of the consistency and general agreement that their results showed with the several reports in the literature, these results could not be totally disregarded.

Very different from the last-described investigation, both in method and in results, was that by Bradford Hill and Galloway (1949), the only prospective type of inquiry as yet reported from Great Britain. This inquiry was based on National Insurance records, and though it fulfilled many of the requirements of a satisfactory investigation it lacked a sufficient number of cases to yield conclusive results, and had no control series. The results are summarized in Table VIII.

Greenberg *et al.* (1949) reported that vaccination against smallpox during pregnancy had no apparent adverse effects upon the child. The children of 4,172 women vaccinated during the first three months of pregnancy included 68 with congenital defects (1.63%). A control series of 2,186 women not vaccinated during pregnancy gave birth to 30 children with congenital defects (1.37%). The authors concluded that the proportions of malformed children in the two groups were not significantly different.

TABLE VIII.—*Summary of the Results Published by Bradford Hill and Galloway (1949)*

Type of Infectious Disease	Infection Occurring During First 3 Months of Pregnancy			Infection Occurring After First 3 Months of Pregnancy		
	No. of Children Born	With Congenital Malformation	Without Congenital Malformation	No. of Children Born	With Congenital Malformation	Without Congenital Malformation
Rubella ..	5	1	4	4	—	4
Measles ..	2	—	2	4	—	4
Infectious hepatitis	—	—	—	1	—	1

Packer (1950) reviewed the literature relating to the influence of maternal measles (morbilli) on the foetus and reported the results of a postal inquiry that he conducted in South Australia into the outcome of pregnancies complicated by measles. There were seven pregnancies in which measles had occurred during the first three months of pregnancy, and these gave rise to one abortion and two live-born children with congenital malformations. The remainder were normal. Eleven other pregnancies in which measles had occurred after the first three months of pregnancy resulted in one abortion and one stillbirth, the others being normal.

Desiderata of a Successful Inquiry

The *prospective* type of inquiry is the only satisfactory approach to the problem of the effects of the virus infections during pregnancy. Nevertheless it must be evident that the various prospective inquiries described above have failed to give conclusive results. It would appear, however, that the more rigorous the technique employed in the inquiry the smaller was the proportion of malformations ascertained to have followed the maternal virus infection. In conclusion, therefore, it may be helpful to state what in my opinion are the desiderata of an inquiry that will yield statistically convincing results.

1. As has been pointed out, the inquiry should be *prospective*, directed forward from the pregnancy to the condition of the child; that is to say, knowledge of the presence or absence of abnormality in the child should not be allowed in any way to influence the selection of cases to be studied. Preferably the selection of each case should have been made before the child was born.

2. The inquiry should provide for the inclusion of cases of rubella, or of any other virus infection that it is proposed to study, occurring at all stages of pregnancy from the earliest weeks.

3. The occurrence of the virus infection should be recorded during the course of the pregnancy, no cognizance being taken of cases in which the occurrence of the infection was not recorded until after the child was born.

4. The diagnosis of the virus infection should have been made by a medical practitioner.

5. The outcome of the pregnancy should be recorded, whether the pregnancy terminated in abortion (including miscarriage), stillbirth, or live birth, and the presence of congenital malformation noted. Live-born children should be examined periodically for a number of years. The cause of abortion or stillbirth and the cause of death of a live-born child should be recorded.

6. A control series should be selected and studied in which the selected virus infections did not occur during pregnancy, precisely similar arrangements being made for ascertaining the outcome of the pregnancy as were made for cases in which virus infection did occur.

7. The medical examination of each child should be carried out, so far as is practicable, on a uniform pattern, and the examiner preferably should not know the maternal history—that is, whether the child had been born from a virus infection or a control pregnancy.

8. The number of virus infection cases and of controls should be sufficient to yield statistically significant results.

Summary

The incidence of congenital malformations is discussed utilizing evidence from mortality and stillbirth statistics and from special studies reported in the literature.

The published results of various *prospective* inquiries into the influence of virus infections during pregnancy in causing congenital malformations are reviewed, and desiderata of a successful inquiry are suggested.

REFERENCES

Abel, S., and Van Dellen, T. R. (1949). *J. Amer. med. Ass.*, **140**, 1210.
Aycock, W. L., and Ingalls, T. H. (1946). *Amer. J. med. Sci.*, **212**, 366.
British Medical Journal (1950). **2**, 122
Carter, C. O. (1951). *Eugen. Rev.*, **43**, 83.
—— and Tizard, J. P. M. (1951). *British Medical Journal*, **1**, 301.
Fox, M. J., and Bortin, M. M. (1946). *J. Amer. med. Ass.*, **130**, 568.
—— Krumbiegel, E. R., and Teresi, J. L. (1948). *Lancet*, **1**, 746.
Greenberg, M., Yankauer, A., Krugman, S., Osborn, J. J. Ward, R. S., and Dancis, J. (1949). *Pediatrics*, **3**, 456.
Gregg, N. McA. (1941). *Trans. ophthal. Soc. Aust.*, **3**, 35.
Grönvall, H., and Selander, P. (1948). *Nord. Med.*, **37**, 409.
Hill, A. Bradford, and Galloway, T. McL. (1949). *Lancet*, **1**, 299.
Javert, C. T., and Stander, H. J. (1943). *Surg. Gynec. Obstet.*, **76**, 1, 115.
Landtman, B. (1948). *Arch. Dis. Childh.*, **23**, 237.
Malpas, P. (1937). *J. Obstet. Gynaec. Brit. Emp.*, **44**, 434.
Ministry of Health (1949). Reports on Public Health and Medical Subjects No. 94, Chapter III. H.M.S.O., London.
Murphy, D. P. (1947). *Congenital Malformations*, 2nd ed. Lippincott, Philadelphia, London, Montreal.
Naujoks (1938). *Arch. Gynäk.*, **166**, 445.
Ober, R. E., Horton, R. J. M., and Feemster, R. F. (1947). *Amer. J. Publ. Hlth*, **37**, 1328.
Packer, A. D. (1950). *Med. J. Aust.*, **1**, 835.
Penrose, L. S. (1951). *Practitioner*, **166**, 429.
Registrar General for England and Wales (1946, 1947, 1948). Statistical Reviews, Tables, Part I (Medical).
Registrar General for Scotland (1945, 1946, 1947). Annual Reports.
Swan, C. (1949). *J. Obstet. Gynaec. Brit. Emp.*, **56**, 341, 591.
—— Tostevin, A. L., Moore, B., Mayo, H., and Black, G. H. B. (1943). *Med. J. Aust.*, **2**, 201.
Tholen, A. (1946). *Geneesk. Gids*, **24**, 338.
Warkany, J. (1947). *Advanc. Pediat.*, **2**, 1.

A short survey of the broad trends of psychological inquiry and the changes undergone in recent years appeared in the *Times Literary Supplement* of August 24. First comes experimental psychology. Traditionally limited to the analysis of comparatively restricted aspects of human behaviour, the study of more complicated patterns has recently been successfully carried out. Much of this work has been done at the Cambridge Psychological Laboratory, under the direction of Sir Frederic Bartlett. An important series of experiments have been carried out on pilot error. Liability to operational fatigue was studied, and much valuable information has been gained about the organization of skilled activity. Next there is medical psychology, which has had an important influence on present-day conceptions of normal behaviour. Due partly to the difficulties of psycho-analysis, and partly to the fact that physical methods of treatment are often more rapid and reliable, the value of psycho-analysis in mental disorders is relatively low. Thirdly comes social psychology, which is developing fast. Founded in 1947, the Tavistock Institute of Human Relations has been largely responsible for the wide range of empirical researches designed to throw light on the basic processes in group behaviour. Studies have been carried out on the problems of resettlement of repatriated prisoners of war, group tensions in family life, the German character structure, and so on. Lastly, there is the study of individual differences in mental capacity, known as the factorial analysis of ability.

TROMEXAN AND DICOUMAROL

BY

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There is now wide acceptance of the value of anticoagulant therapy. The necessity for prolonged courses of heparin was obviated by the introduction of dicoumarol, which brought the advantages of oral administration and relative cheapness. The disadvantages of dicoumarol, such as its slowness of action, its cumulative toxicity with the attendant risk of haemorrhage, and the necessity for daily prothrombin estimations often caused a hesitancy in employing it. Rosicky (1944) produced a new coumarin drug—bis-3:3'-(4-oxycoumarinyl) ethyl acetate—which is now available as "tromexan" (Geigy). Evidence is accumulating that this drug has advantages over dicoumarol.

Pulver and von Kaulla (1948) observed that in man tromexan disappeared from the blood in 36 hours; with dicoumarol the time lag was five days. They also recorded a method for assessing the tromexan level in plasma. Reinis and Kubik (1948) claimed for tromexan a shorter latent period than that of dicoumarol, easier control, and a more rapid return to normal of the prothrombin level after cessation of treatment. They observed a certain individual variation with regard to tromexan activity and only slight toxicity. Von Kaulla and Pulver (1948) adduced, by animal experiments, evidence supporting these contentions.

Deutsch (1949) observed the production of initial hyperprothrombinaemia in man, as with dicoumarol, while Bickel and Della Santa (1949) put forward a plea for divided dosage and recorded only mild and transient haemorrhagic incidents.

The low toxicity of tromexan was illustrated by the proposal of Della Santa and von Kaulla (1949) to use the effect of the drug on the prothrombin level as a test of liver function, while Lian *et al.* (1950) employed the drug for as long as 11 weeks without tolerance or cumulative toxicity occurring.

With dicoumarol the maximum effect on the prothrombin level may be delayed as long as 72 hours. Burt, Wright, and Kubik (1949) pointed out that the tromexan lag period is usually 8 to 24 hours. According to Burke and Wright (1950) the maximum effect was obtained in 28 to 36 hours, although an appreciable therapeutic effect was reached in 18 to 24 hours, while the prothrombin level returned to normal in 60 to 72 hours. Reinis and Kubik (1948) found that this "hangover" effect might, however, be prolonged up to seven days. It is estimated by Burke and Wright that tromexan has one-sixth the potency and one-twentieth the toxicity of dicoumarol. Experimental evidence has been adduced by Kubik and Reinis (1950) to demonstrate the effectiveness of tromexan in the reduction of intra-arterial clot. All publications claim for the drug relative safety and good clinical results.

Administration and Control of Tromexan Therapy

The drug is administered orally in tablets of 300 mg., which are grooved to facilitate smaller dosage. In the present series no patient complained of the taste of the drug, and there was no gastric upset.

Prothrombin estimation was achieved by Quick's method, using human brain as a source of thromboplastin. It was found to be an advantage, though usually impracticable, to have a reading before starting treatment. In the absence of complicating factors these initial readings varied between 60 and 100%. With congestive cardiac failure preliminary readings as low as 45% were recorded. Adjustment of the initial loading dose was therefore necessary.

A therapeutic level of between 30 and 10% of normal prothrombin was aimed at and a course of three weeks' duration envisaged, as with dicoumarol. A loading dose of 1,200 mg. proved safe and became standard, although 2,100 mg. was given twice without incident. All cases of pulmonary embolism and those of cardiac infarction with marked systemic upset were given heparin initially. At the outset of the investigation an intravenous drip of normal saline with 300 mg. of heparin was provided concomitantly for the first 24 hours, as this was thought to be the average tromexan lag period. In three out of five cases, however, a prothrombin concentration of less than 10% resulted within 24 hours. Latterly there was evolved the plan of giving one intravenous dose of 100 mg. of heparin along with the loading dose of tromexan. Multiple divided doses of heparin in the first 24 hours of treatment were found not only unnecessary and economically wasteful but they apparently invoked a complicating factor in prothrombin depression, for which allowance had to be made in estimating tromexan dosage.

Between 12 and 24 hours after starting treatment, and before further tromexan was administered, a prothrombin concentration test was performed: 70% of the cases were found to have less than 50% prothrombin, and 34% had entered the therapeutic range of 10 to 30% prothrombin. A few cases showed resistance to the drug and two demonstrated an initial increase in prothrombin.

At this point it should be made clear that before starting the course of tromexan it is impossible to forecast the dosage necessary for a given patient to enter or remain in the therapeutic zone. Age and body weight give no assistance, and even the response to the loading dose is occasionally deceptive in that a high degree of drug resistance may be soon overcome with intensive dosage, and minimal doses suffice thereafter.

Subsequent to the loading dose the daily ration was divided into two or three doses, but no tromexan was given until each morning's prothrombin value was to hand. A technique of trial and error was employed, although usually the necessary maintenance dose lay between 300 and 600 mg. Two patients were well controlled on a daily average of 150 mg.; two others required between 900 and 1,200 mg. each day. No case was maintained on a constant daily dosage. A rough guide to dosage is given in Table I.

TABLE I

Prothrombin Concentration	Daily Ration of Tromexan
100–80%	1,200 mg.
80–60%	900–750 mg.
60–40%	750–600 ,,
40–20%	600–300 ,,
20–10%	300–150 ,,
Under 10%	0

Unfortunately, most patients exhibited a sudden escape from control after being well maintained for several days. This seldom took the form of a dangerous drop in prothrombin, but consisted of a sudden rise requiring increased dosage to recover equilibrium.

There is therefore no escape from frequent, preferably daily, prothrombin estimations. It is significant that in association with these episodes of apparent drug resistance were recurrences of ischaemic pain in the cardiac cases, and in one case a fresh cardiac infarction. The basic defect in such incidents is possibly in intestinal absorption of the drug, and it may be that inactivation takes place under certain intestinal conditions.

Depression of the prothrombin concentration below 10% was not infrequent, usually in the first days of treatment. It gave rise to little of the concern that one felt when dicoumarol was being used as the anticoagulant. Of the 72 cases treated with tromexan only one who reached the "danger-zone" bled, when haematemesis resulted from an active duodenal ulcer. Dicoumarol compares unfavourably in this respect, and it seems unwise to assess the patient's reaction to the coumarin drugs purely on prothrombin levels (Bickel and Della Santa, 1949).

Frequent search was made for microscopical haematuria. Bleeding incidents occurred in two of the 72 patients treated. Both suffered a haematemesis from a clinically active duodenal ulcer. One of these had a prothrombin concentration of less than 10%, which was regarded formerly as dangerously low. The other was in the centre of the therapeutic range, however. Neither case required any more active treatment than the cessation of tromexan therapy. It is considered that in the presence of peptic ulceration tromexan should be used with caution. A serious haemorrhage may be anticipated, and possibly averted, by the use of frequent benzidine tests of the faeces of such patients.

After the last dose of tromexan the prothrombin level was followed in 20 patients. The average time for recovery was 60 hours, the extremes being 14 hours and 14 days. Prolongation of action could not be correlated with delayed initial effect or drug resistance (Burt *et al.*, 1949).

Results of Tromexan Therapy

(*a*) *Cardiac Infarction.*—Sixty cases of cardiac infarction were treated (Table II). Confirmation of the clinical diagnosis was obtained by electrocardiogram or necropsy in all. Fifty-one cases left hospital, the immediate end-result being satisfactory. Nine patients died in hospital, but two of these succumbed after the cessation of treatment—one from pneumonia and the other from renal failure secondary to gross atheroma and hypertension. Of the remaining seven who died, each of whom had suffered an anterior infarction, one died twelve hours after admission with haemopericardium and ventricular rupture. Two others, who died within a few days, had rupture of the left ventricle, while another two came to necropsy with previous multiple infarcts and a grossly scarred myocardium. Necropsy was refused in one aged woman who succumbed after attacks of acute left ventricular failure. A cerebro-vascular accident was coincident. The remaining fatal case never entered the therapeutic range of prothrombin. Sudden death occurred on the seventeenth day of treatment, and necropsy revealed a large infarct which had probably slowly extended.

TABLE II.—*Results*

	Anti-coagulant	No. of Cases	Discharges	Hospital Deaths	Bleeding Manifestations
Cardiac infarction	Tromexan	60	51	9	2
	Dicoumarol	36	29	7	7
Extracardiac thrombosis	Tromexan	12	12	0	0
	Dicoumarol	22	19	3	6

(*b*) *Extracardiac Group.*—Twelve cases of extracardiac thrombo-embolic incidents received tromexan. Six suffered from phlebothrombosis, while six had also sustained a pulmonary embolus. The end-result was regarded in all as satisfactory.

Bleeding Incidents.—Among these 72 patients, as previously recorded, there were two cases of haematemesis in duodenal ulcer sufferers. The only necessary measure was the withdrawal of tromexan.

Results of Dicoumarol Therapy

(*a*) *Cardiac Infarction.*—Thirty-six cases of cardiac infarction were treated (Table II). The clinical diagnosis was confirmed in 35. In one case the electrocardiogram was normal but the diagnosis indisputable. Twenty-nine cases left hospital, the immediate end-result being satisfactory. Two patients died after the cessation of dicoumarol—one from a recurrence of infarction, the other from pneumonia. The remaining five who succumbed during treatment had sustained anterior infarcts. One died from a recurrence while in the therapeutic range of prothrombin. A further death occurred 36 hours after admission with extensive and recurrent infarcts and gross cardiac failure. One who died suddenly had a grossly scarred left ventricle, which was freshly infarcted while the patient was in the therapeutic range. Gross scarring was likewise noticed in a further patient who suffered profuse haematuria till the time of death in spite of transfusion. The last had suffered what was clinically ventricular rupture. No necropsy was permitted.

(*b*) *Extracardiac Group.*—Twenty-two cases of extracardiac thrombo-embolic incidents received dicoumarol. Eleven suffered from phlebothrombosis alone; seven had also sustained a pulmonary embolus. Four had developed peripheral arterial obstruction. Nineteen left hospital with an end-result regarded as satisfactory. Of the three deaths, two occurred after the cessation of therapy—one from renal carcinoma, the other from cerebral thrombosis. The third patient died during the dicoumarol treatment of a pulmonary embolus. The main cause of death was prolonged epistaxes and haematuria which failed to respond to transfusion.

Bleeding Incidents.—Of the 58 patients who received dicoumarol 13 bled. Five of these were not out of control as judged by prothrombin levels. Three lost blood from several orifices simultaneously. Haematuria occurred in nine, epistaxes in four, melaena in two, while there was one case of haematemesis and one of subcutaneous bleeding. All received intravenous vitamin K, and three required transfusion. Two of those who bled succumbed; the haemorrhage was an important factor in their death.

Conclusions

Tromexan in clinical practice is superior to dicoumarol. As it has a shorter "lag period" the use of heparin may be either obviated or restricted to a single intravenous dose, with great economic benefit.

The clinical results compare favourably with those of dicoumarol therapy; indeed, the fatal cases, with the exception of one patient who was inadequately treated, were poor risks. Haemorrhagic complications are not only less frequent but infinitely less severe. A striking

comparison is possible in the effects of a fall in prothrombin concentration below 10%, which was regarded in the tromexan group with relative equanimity.

None of the cardiac patients receiving tromexan suffered a recurrence of ischaemic pain while in the therapeutic range of 10 to 30% prothrombin. Two patients in the 40 to 50% range sustained further thrombotic episodes, and the return of ischaemic cardiac pain, not amounting to infarction, was always coincident with inadequate dosage. Two of the cardiac cases receiving dicoumarol developed fresh infarctions while ostensibly admirably controlled.

There were marked variations in susceptibility to tromexan. Indeed, a given patient's tolerance may alter widely from day to day, and there is a tendency to sudden escapes from control. It is therefore not desirable to give the drug without laboratory control. No correlation of dosage with weight or age is possible, but an initial prothrombin reading may assist in gauging the size of the loading dose.

Caution is necessary in treating peptic ulcer patients. Benzidine tests on the faeces may be helpful in the control of their treatment.

Summary

Clinical results are recorded in 130 patients suffering from vascular thrombosis and its sequelae.

Ninety-six of these had sustained a cardiac infarct. Sixty received tromexan and 36 dicoumarol.

A scheme for the use of tromexan is proposed and the literature briefly reviewed.

I wish to express my thanks to Dr. H. N. Robson, who suggested this investigation; to the physicians and surgeons of the Northern Hospitals Group, Edinburgh, who permitted access to their patients; and to the staff of the haematological laboratory for technical assistance. The tromexan was supplied by Pharmaceutical Laboratories, Geigy Ltd., Manchester.

REFERENCES

Bickel, G., and Della Santa, R. (1949). *Rev. méd. Suisse rom.*, **49**, 545.
Burke, G. E., and Wright, I. S. (1950). *Bull. N.Y. Acad. Med.*, **26**, 264.
Burt, C. C., Wright, H. P., and Kubik, M. (1949). *British Medical Journal*, **2**, 1250.
Della Santa, R., and von Kaulla, K. N. (1949). *Helv. med. Acta*, series A, **16**, 251.
Deutsch, E. (1949). *Schweiz. med. Wschr.*, **79**, 1010.
Von Kaulla, K. N., and Pulver, R. (1948). Ibid., **78**, 806.
Kubik, M., and Reinis, von Z. (1950). International Congress of Haematology, Cambridge.
Lian, C., Siguier, F., Welti, J. J., Piette, M., Coblentz, B., and Trélat, J. (1950). *Bull. Soc. méd. Hôp. Paris*, **66**, 110.
Pulver, R., and von Kaulla, K. N. (1948). *Schweiz. med. Wschr.*, **78**, 956.
Reinis, von Z., and Kubik, M. (1948). Ibid., **78**, 785.
Rosicky, J. (1944). *Cas. Lék. ces.*, **83**, 1200.

In New York during the 32 years 1918–50 there were 104 fatal injuries from competitive sports, and 73 post-mortem examinations were made. Writing in the *Jou.nal of the American Medical Association*, August 18, page 1506, Dr. T. A. Gonzales discusses the kinds of lethal injury sustained in different sports and their frequency, without, unfortunately, stating the numbers at risk in each activity. There surely cannot be many people in New York who play cricket, for instance, yet one death is recorded in this game—that of a player struck in the abdomen by a ball which ruptured the small intestine and led to acute peritonitis. This must be as rare a cause of death in England as that of the relay runner who ran into a railing alongside the track and ruptured his large bowel. Baseball has the highest total, with 43 deaths, and football (with 22 fatalities) was about level with boxing (21): but surely there are fewer boxers than football players in New York City?

DOSAGE OF PENICILLIN IN WEIL'S DISEASE

BY

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Penicillin has been used for some years in the treatment of Weil's disease (leptospirosis icterohaemorrhagica), and its efficacy, especially in the pre-icteric stage of the disease, is generally accepted. There is, however, wide variation in the dosage recommended. Chang (1946) recommended a total daily dosage of 250,000–300,000 units of sodium penicillin. Patterson (1947) used three-hourly injections of 15,000 units. Suchett-Kaye (1951) used 100,000 units four-hourly and raised the dose to 500,000 units four-hourly if the patient's condition warranted it. The following cases illustrate some of the important clinical aspects of the disease and lend support to the use of a dosage of the order recommended by Suchett-Kaye.

Case 1

A butcher aged 32, who had bathed several times in a canal during the three weeks preceding his illness, was admitted on the sixth day of the disease, having had severe pains in the limbs for five days and frequent vomiting for three days.

He was a big, well-nourished man, obviously ill, with a temperature of 102.6° F. (39.2° C.). He had an erythematous rash on the face and trunk. There was marked suffusion of the conjunctivae, which were bright red. Jaundice was not present. The tongue was coated and dry. Slight neck rigidity was present, but Kernig's sign was negative. The muscles of the thighs and forearms were tender. The liver was not palpable, but he was tender in the right hypochondrium. The spleen was not palpable. His blood pressure was 110/80. The rest of the physical examination was negative. A provisional diagnosis of Weil's disease was made and various confirmatory tests were carried out. The urine contained a moderate amount of albumin, but was otherwise normal. The haemoglobin was 84%; white cells, 2,900 (polymorphs 74%, lymphocytes 22%, monocytes 4%); serum bilirubin, less than 0.5 mg. per 100 ml.; blood urea, 165 mg. per 100 ml. N.P.N., 97 mg. per 100 ml. A radiograph of the chest was normal. Blood taken at the time of admission for agglutination for *Leptospira icterohaemorrhagiae* was later reported as negative.

Soon after admission, before penicillin was started, his temperature rose to 104.8° F. (40.5° C.) and he became delirious and hallucinated, seeing people moving on the wall. Penicillin was therefore begun in doses of 30,000 units four-hourly by intramuscular injection. Thirty-six hours later his condition had not improved much, though his temperature was a little lower and he was no longer hallucinated. He was very drowsy. The dosage of penicillin was therefore increased to 100,000 units six-hourly. After this his temperature fell to normal over the next 48 hours and his clinical condition rapidly improved. This dosage was continued for eight days until a total of 3,500,000 units had been given. Convalescence was uneventful apart from a mild attack of gout in the left great toe on the eleventh day of the disease. He had never had gout before, but his mother suffered from it.

Blood taken on the eleventh day of the disease gave positive agglutinations for *L. icterohaemorrhagiae* at a dilution of 1/3,000.

Case 2

A hosiery packer aged 17, who had often bathed in a river during the month preceding his illness and whose workplace was infested with rats, was admitted on the third day

of the disease complaining of headache, feverishness, and severe pains in the back and limbs. His mother said that he had become increasingly drowsy and mentally confused since the onset of the illness three days before.

He was a well-nourished boy. His temperature was 101° F. (38.3° C.). He was drowsy and uncooperative, resenting examination. There was no rash, but the conjunctivae were markedly inflamed. Jaundice and neck rigidity were not present, and Kernig's sign was negative. The liver and spleen were not palpable. There was no hepatic tenderness. The remainder of the physical examination was negative. His blood pressure was 120/80. Lumbar puncture gave a clear colourless fluid with a normal pressure. The C.S.F. examination showed: total protein, 40 mg. per 100 ml.; globulin, slightly increased; chlorides, 728 mg. per 100 ml.; cells, 24 per c.mm. (mainly lymphocytes). The blood showed a slight leucocytosis of 11,200 per c.mm. (polymorphs 86%, lymphocytes 12%, monocytes 2%). The urine contained a trace of albumin, but was otherwise normal. The blood urea was 55 mg. per 100 ml. *X*-ray examination of the chest was normal.

Penicillin, 250,000 units three-hourly by intramuscular injection, was begun. The temperature, after an initial rise to 104° F. (40° C.) became normal after 12 hours, and remained so. A total of 14,000,000 units of penicillin was given over the next seven days. Convalescence was uneventful and he made an uninterrupted recovery. Blood taken on the fourth day of the disease gave negative agglutinations for *L. icterohaemorrhagiae*, but blood taken on the eleventh day was positive at 1/3,000 for *L. icterohaemorrhagiae* and at 1/300 for *L. canicola*.

Case 3

A schoolboy aged 13, who had no known contact with rats but who had recently paddled in a stream several times, was admitted with a seven-day history of malaise, pyrexia, anorexia, and vague pains in the limbs. His eyes had become red on the day of admission. He was slightly lethargic and had a temperature of 101° F. (38.3° C.). The tongue was coated. Enlarged glands were present in the neck, axillae, and groins. The conjunctivae were moderately inflamed. The liver and spleen were not palpable. There was no meningism. His blood pressure was 110/75; E.S.R., 10; white cells, 6,000 (polymorphs 54%, eosinophils 4%, lymphocytes 42%); Paul–Bunnell reaction, titre 1 in 32. The urine was quite normal and contained no albumin.

He did not appear at all ill, and after 24 hours in hospital all his symptoms disappeared and the temperature became normal without any treatment. The true nature of his illness was not clear until the blood agglutinations, from a specimen taken on admission, were reported as positive at 1/10,000 for *L. icterohaemorrhagiae*. He was then given a four-day course of 250,000 units of penicillin three-hourly.

Case 4

This patient, a sheet-metal worker aged 18, had an unusual history. He had been feeding his hens 10 days before admission, when a rat ran up his trouser leg and bit him on the right buttock. Seven days later he had aching limbs and an occipital headache, was feeling cold, and was shivering. He later developed dull upper abdominal pain, and on the tenth day after the bite he became jaundiced and was admitted to hospital. His urine had been dark and his stools rather pale.

On examination he was seen to be a well-nourished youth with a moderate degree of jaundice. A small healing wound was present on the right buttock close to the sacrum. His temperature was 102° F. (38.9° C.), pulse 130 a minute, and respirations 27 a minute. The conjunctivae were moderately inflamed. The tongue was clean. No rashes were present. There was no abdominal tenderness. The liver, spleen, and lymph glands were not enlarged. The remainder of the physical examination was negative. The urine contained a large amount of albumin and bile; granular and cellular casts were present. Blood urea was 134 mg. per 100 ml.; serum bilirubin, 16.2 mg. per 100 ml.; thymol turbidity, 3 units. An initial dose of 100,000 units of penicillin was given, followed by 50,000 units three-hourly by intramuscular injection, but his condition deteriorated. He became increasingly drowsy and jaundiced over the next seven days and had epistaxis, haemoptysis, and melaena. Intravenous glucose, saline, and vitamin K were given, but he died on the seventh day from what was clinically liver failure.

At necropsy the liver, spleen, and kidneys were pale, soft, and swollen. The lungs showed considerable oedema, with a macroscopic appearance suggestive of a haemorrhagic bronchopneumonia. There was flattening of the convolutions of the brain with engorgement of the superficial vessels. A smear taken from the liver showed many active leptospires on dark-ground illumination. Microscopically the brain showed generalized vascular engorgement. The liver and kidneys showed a fairly marked degree of cloudy swelling but were not grossly abnormal. The lungs showed a haemorrhagic bronchopneumonia. Blood taken on admission gave positive agglutinations for *L. icterohaemorrhagiae* at 1/10,000.

Discussion

As many writers, notably Broom and Alston (1948), have now pointed out, infection with *L. icterohaemorrhagiae* may be commoner than is generally recognized. It is by no means confined to those who are exposed to infection as an industrial hazard. Agglutination tests for this organism might well form part of the routine investigation of a case of P.U.O., especially in those parts of the country where the disease is known to be endemic. It it important that the diagnosis should be made and treatment begun as soon as possible (Smith, 1949).

The diagnosis in the first instance must be a clinical one, because jaundice, if it occurs, is a late phenomenon; because there may be a leucopenia rather than a leucocytosis in the early stages; because albuminuria may at first be slight or even absent; and because the agglutinations do not become positive until about the ninth day (Smith, 1949). The blood urea and non-protein nitrogen may begin to rise early, especially in the more severe cases. Smith states that the organism can always be recovered in the first four days by intraperitoneal injection of a guinea-pig with fragmented blood-clot, but the method takes time. Examination of the cerebrospinal fluid may help, as this is frequently altered (Cargill and Beeson, 1947), the main change being in the cell count, which may rise to 50–300 cells per c.mm., with varying proportions of granulocytes and lymphocytes (Buzzard and Wylie, 1947).

Clinically, Weil's disease should be considered in influenza-like illnesses in which there is marked reddening of the conjunctivae and severe pains in the limbs. The muscles may be distinctly tender, and slight neck rigidity may be present but not Kernig's sign (Buzzard and Wylie, 1947). The disease should also be thought of in cases presenting as aseptic meningitis, as in Buzzard and Wylie's series. Patterson (1947) noted that eye complications in the form of iritis, iridocyclitis, and uveitis sometimes occur one month to one year after the acute infection, so that if the original illness is not diagnosed the true nature of these complications may be difficult to explain.

Bulmer (1945) stated that the value of penicillin in Weil's disease can be assessed only by observing its effect during the pre-icteric phase. Cases 1 and 2 fall into this category. Case 1 showed little response to 30,000 units of penicillin four-hourly. The response on raising the

dose to 100,000 units six-hourly was quite dramatic and a rapid improvement set in. Case 2 received 250,000 units three-hourly. After the first dose there was a sharp rise of temperature from 100 to 104° F. (37.8 to 40° C.), the patient became violent and abusive, and he had to be given a sedative. Thereafter he improved rapidly and the temperature was normal by next morning. Suchett-Kaye drew attention to a reaction resembling the Jarisch–Herxheimer reaction which may occur at the beginning of treatment of Weil's disease with penicillin.

Case 1 showed a slight rise of temperature, which might or might not have been of significance. In Case 2 the reaction was marked. Prognostically it may be regarded as a favourable sign, as it may mean that the strain of organism is sensitive to penicillin and is being destroyed. Case 4 showed no such reaction, and he went steadily downhill. He was jaundiced on admission, but his general condition was good. He received 100,000 units of penicillin initially and 50,000 units three-hourly thereafter. Necropsy revealed two striking features. The first was that neither macroscopically nor microscopically did the brain, lungs, liver, or kidneys appear to be irreparably damaged. The second was that a smear from the liver showed so many leptospires. One was left with the impression that had it been possible to destroy the organisms a few days earlier the outcome might not have been fatal.

Case 3 had recovered spontaneously, but a course of 250,000 units of penicillin three-hourly was given for four days with the object of avoiding the carrier state or the possibility of smouldering renal damage. Patterson found that in his cases a large number of leptospires continued to be excreted in the urine for many weeks after clinical recovery.

Summary and Conclusions

Four cases of Weil's disease treated with penicillin are described, including one which was presumably contracted by actual rat-bite.

The diagnosis in the first instance is a clinical one, and treatment should be started without delay.

The dosage of penicillin recommended is 250,000 three-hourly by intramuscular injection. If there is no favourable response after 24 hours it may be advisable to try doubling the dose. Penicillin should be continued until the patient is clearly out of danger—usually at least a week.

A rise of temperature after the initial doses of penicillin would appear to be a favourable sign.

A four-day course of penicillin in this dosage might reasonably be given to spontaneously recovering cases in order to avoid the carrier state.

I wish to thank Dr. J. P. W. Jamie, Dr. W. D. Jeans, and Dr. S. E. Tanner for permission to use their cases.

REFERENCES

Broom, J. C., and Alston, J. M. (1948). *Lancet*, **2**, 96.
Bulmer, E. (1945). *British Medical Journal*, **1**, 113.
Buzzard, E. M., and Wylie, J. A. H. (1947). *Lancet*, **2**, 417.
Cargill, W. H., and Beeson, P. B. (1947). *Ann. intern. Med.*, **27**, 396.
Chang, S. L. (1946). *J. clin. Invest.*, **25**, 752.
Patterson, H. M. (1947). *J. Amer. med. Ass.*, **134**, 1077.
Smith, J. (1949). *Brit. J. industr. Med.*, **6**, 213.
Suchett-Kaye, A. I. (1951). *Lancet*, **1**, 90.

A British Standard for hospital bedside lockers has been prepared by a technical committee representative of medical and nursing interests and manufacturers of wood and metal lockers. It indicates the kind of articles—for example, food, toilet requisites, personal effects, etc.—for which the locker should provide separate accommodation and the minimum space to be allotted to each kind of article.

ERGOT POISONING AT PONT ST. ESPRIT

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The outbreak of poisoning at Pont St. Esprit has drawn attention again to ergot of rye. Old accounts are concerned chiefly with repeated poisoning; here absorption of the poison was a single though major event. The frequent occurrence of mental symptoms has again called to mind the old name of the disease, "Mal des Ardents."

Alimentary poison was immediately suspected because of the large number of people attacked. It was easy to incriminate the bread, the more so because animals which ate some of the poisoned bread died making convulsive movements. From the first, ergotism seemed very probable. Setting aside the problems posed by the presence in bread of this poison, alone or associated with others, we shall briefly describe the symptoms observed during the first 15 days. The disturbances can be divided into four phases.

The First Symptoms

Absorption took place during a single day (for most, August 15). The bread certainly contained a high proportion of poison, for the amounts eaten were often very small. The first symptoms appeared after a latent period of 6 to 48 hours. In this first phase, the symptoms were generalized, and consisted in a depressive state with anguish and slight agitation. After some hours the symptoms became more clearly defined, and most of the patients presented with digestive disturbances. Particularly notable was the state of nausea, with diffuse abdominal pain; less often noted were vomiting and diarrhoea (in about 30% of cases). There was often a sensation of distressing pharyngeal constriction.

Disturbances of the autonomic nervous system accompanied the digestive disorders—gusts of warmth, followed by the impression of "cold waves," with intense sweating crises. We also noted frequent excessive salivation. The patients were pale and often showed a regular bradycardia (40 to 50 beats a minute), with weakness of the pulse. The heart sounds were rather muffled; the extremities were cold. The temperature of most of the patients was low, both in the morning and in the evening (36.5–36.8° C. (97.8–98.2° F.)). Arterial tension was in general rather low. In some patients we noted a disquieting fall in pressure during fainting attacks. Mydriasis was very frequent, with diminution of the light reflex. Some patients complained of pain at the nape of the neck, more rarely of true headaches.

Thereafter a constant symptom appeared—insomnia lasting several days. The digestive disorders quickly became worse, and there was diffuse or subhepatic abdominal pain, with burning sensations throughout the whole of the digestive tract. They were accompanied by frequent colicky pains, and some experienced sensations of burning at the anus. A state of giddiness

persisted, accompanied by abundant sweating and a disagreeable odour. The special odour struck the patient and his attendants. These pale and limp patients showed inconspicuous trembling of the extremities: they complained of disorders of visual accommodation and especially of being unable to read.

The Severe Cases

For many of these patients the illness went no further than that: after suffering from insomnia for several days, the ability to sleep again was the sign of their recovery. For the others, remission of digestive disorders was only a 48-hours lull before the appearance of more characteristic signs. Even about six days afterwards, in some of the patients, more severe disorders appeared, and the vasomotor phenomena became worse. Formication, with pallor and cold in the extremities, recalled Raynaud's syndrome. Hands and feet were equally attacked; painful paraesthesias and cramps of the calves followed, aggravated by the weight of the sheets. Some of the patients had severe fainting attacks with imperceptible pulse, low and feeble arterial tension, and a feeling of anguish which often went spontaneously. Between these crises we noticed in some cases hypertensive attacks (190/100 mm. Hg); they seemed to be generalized vasomotor crises.

Neurological examination was poor but showed most often the following signs: intentional tremor was nearly always found; it was sometimes accompanied by fibrillary twitching, and there was a suggestion of myoclonus. In several unusual cases there seemed to be a cerebellar syndrome. Romberg's sign was never seen. The reflexes were slightly exaggerated, especially the patellar. In six cases we noticed a transient Babinski reflex. There was no paralysis. The mydriasis disappeared, but accommodation remained difficult.

Logorrhoea, psychomotor agitation, and absolute insomnia always presaged the appearance of mental disorders. Towards evening visual hallucinations appeared, recalling those of alcoholism. The particular themes were visions of animals and of flames. All these visions were fleeting and variable. In many of the patients they were followed by dreamy delirium. The delirium seemed to be systematized, with animal hallucinations and self-accusation, and it was sometimes mystical or macabre. In some cases terrifying visions were followed by fugues, and two patients even threw themselves out of windows. The delirium was of a confusional kind which could be interrupted for some moments by strong stimulation. Every attempt at restraint increased the agitation. In severe cases muscular spasms appeared, recalling those of tetanus, but seeming to be less sustained and less painful. During this stage, sweating was abundant, and the temperature somewhat raised. The duration of these periods of delirium was very varied. They lasted several hours in some patients, in others they still persist. As the illness developed, certain visceral signs were noted: albuminuria, sometimes with haematuria. On the other hand, the blood urea often rose to 60–120 mg. per 100 ml.

Fatal Cases

Such were the signs observed in general. Many of the patients did not show the signs and symptoms in their entirety. Most of the cases were limited to digestive disorders, insomnia, and slight disturbance of the autonomic nervous system. About 25 cases were of the severe delirious form. We observed four fatal cases—three men and one woman. Three of these people were old and in bad health. The woman had hyperthyroidism. One of the men was only 25 years old and had been in good health previously. They died in muscular spasm and in a state of cardiovascular collapse. The blood urea was raised to 150 mg. per 100 ml. The woman showed at her death a moist gangrene of the toes.

The disorders developed more quickly in children, but also left them more quickly. In two cases we observed epileptiform convulsions, controlled by barbiturates.

An interesting feature of some cases was that the delirium was the first serious sign to be noted; it then appeared very late—between 10 to 12 days after the first onset of poisoning. It is difficult to know just how many people presented with only slight disorders—disturbances of digestion and sleep—but it was about 150. A pregnant woman was seen with frank haemorrhages, and several women menstruated prematurely.

Now that we have gathered the documents together, 15 days after the poison was taken, it is still too soon to give a definite balance sheet. Nevertheless, we can foresee the complete disappearance of the vascular disorders, but we cannot say what the effect will be on the minds of some of the patients, in particular on the minds of alcoholics who fell victims to the poison.

Medical Memoranda

Deafness from Dihydrostreptomycin

In the *American Review of Tuberculosis* of January, 1951, there appears a note on an article about "Lange Kuren" by J. E. Minkenhof (*Ned. Tijdschr. Geneesk.*, 1950, **94**, 2129). In this note it is stated that dihydrostreptomycin is more toxic than streptomycin; at the same dosages it was found that in adults, but not in children, dihydrostreptomycin caused partial to total deafness in a very high percentage of patients. The statement warrants widespread publicity; for, to say the least of it, it is most distressing to save a child from tuberculous meningitis only to render him or her totally deaf, especially if this can be avoided.

Material

In August, 1949, a 25-bed unit was established in this hospital for the treatment of tuberculous meningitis and miliary tuberculosis. Thirty cases of the former have been treated and four cases of the latter. Intensive antibiotic therapy has been used in all cases. For an adult with meningitis the course of treatment was: First course, 2 g. daily in two doses by intramuscular injection for four months, and 100 consecutive intrathecal injections of 50 mg. daily. A rest period was then given which varied from 14 to 28 days, depending on the rapidity of response to the first course. The second course consisted of 2 g. daily in two doses by intramuscular injection for three months, and 50 intrathecal injections of 50 mg. at two-day intervals. Appropriate reductions in dosage were made according to age and not

to individual body weight, a standard reduction being made for each age group. This was done to facilitate the work of the ward staff by reducing the number of variations of dosage to the smallest possible.

For an adult with miliary disease without meningitis a four-months intramuscular course of 2 g. streptomycin daily was given. This was followed by a rest period of one month and a second course of intramuscular streptomycin for one month. P.A.S. was usually given throughout the stay in hospital.

In July, 1950, dihydrostreptomycin replaced streptomycin in the hospital.

Analysis of the 34 Cases Treated

		Death	Recovery
Tuberculous meningitis	Treated with streptomycin	3	14
	Treated with dihydrostreptomycin	5	8
Miliary tuberculosis	Treated with streptomycin	—	3
	Treated with dihydrostreptomycin	—	1

All the recovered cases treated with streptomycin have now been discharged, except two who are still in hospital simply because home conditions are unsuitable. All these cases have been carefully followed up to the present and every patient can hear a forced whisper at 12 feet without any difficulty. It may be stated that the services of an otologist have not been available, and a scientific assessment of hearing acuity has therefore not been possible.

Cases of Deafness

Of the cases treated with dihydrostreptomycin, there have been four in whom marked impairment of hearing has occurred either during treatment or soon after the completion of treatment.

Case 1.—A girl aged 17. She responded to treatment slowly, and a positive culture of tubercle bacilli was obtained four months after the beginning of treatment. At about the fifth month of treatment she became totally deaf within 14 days. No evidence of other cranial nerve involvement of any kind has ever been obtained. She now appears well, though she continues on treatment. She remains totally deaf.

Case 2.—A girl aged 6 years. She made an uninterrupted recovery from her meningitis without incident. During the second month of her second course of treatment with dihydrostreptomycin she became totally deaf within four days.

Case 3.—A girl aged 8 years. She made an uninterrupted recovery without incident and was first noted to be partially deaf one month after discharge from hospital at her re-examination.

Case 4.—A boy aged 8 years. He also made an uninterrupted recovery, but was first noted to be partially deaf at re-examination one month after discharge from hospital.

Comment

The degree of deafness in all four cases is now gross. It is a nerve deafness. The loss of hearing in the first two cases was extremely rapid. In the second two cases it seems likely that it has been extremely slow. We now feel that the impairment of hearing probably began during treatment, but that the degree of impairment remained so slight that it was not detected by our crude tests until one month after discharge. This suggests that, once the auditory nerve has been damaged by the drug, progressive impairment of hearing may occur after all dihydrostreptomycin therapy has ceased.

Case 1 did not respond satisfactorily to treatment, and it was at first felt that her deafness might be attributable to the meningeal process. However, the response to treatment in the other three cases was highly satisfactory. In none of these four cases has there ever been any evidence of paresis of other cranial nerves.

Case 3 has recently been seen by an otologist, who states that a gross degree of nerve deafness is present, but that this could result from the meningeal process. However, it is striking that among 14 recovered cases treated with streptomycin there has been no case of deafness of any degree. Also, in three of the cases in which deafness has occurred after treatment with dihydrostreptomycin the impairment of hearing has appeared late in the course of treatment or after treatment was completed, and it seems unlikely that the meningeal process can therefore be blamed. Only one case of miliary tuberculosis has been treated with dihydrostreptomycin, and without evidence of impairment of hearing.

The evidence therefore strongly suggests that the deafness has been caused directly by the dihydrostreptomycin. There appear to be no grounds for continuing to treat cases of tuberculous meningitis with dihydrostreptomycin rather than streptomycin.

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Case of Coma Associated with Ketonuria in a Young Adult

The following case seems to be unusual enough to merit recording.

Case Report

A male student, aged 22, at a teachers' training college was admitted to hospital on January 16, 1951, as an emergency in a state of semi-coma. Thirty-six hours previously he had been taken ill, with colicky abdominal pains, had vomited twice, and subsequently had felt better. He slept well that night. Next morning he became stuporous and was difficult to rouse. The colicky abdominal pains returned. He had had no bowel action for two days.

When seen after admission he was lying in a comatose condition on his side with his knees drawn up. There was marked air hunger, and his breath smelt strongly of acetone bodies. His temperature was 98.4° F. (36.9° C.), pulse 70, and respirations 22. He could be roused, but his cerebration was slow, and he answered only in monosyllables and at once relapsed into coma. His tongue was coated and dry; his colon was loaded. His urine gave strongly positive reactions to the ferric-chloride and Rothera tests, but no albumin or sugar was present. His other systems revealed no abnormality. His appearance was that of a diabetic coma, but his blood sugar was 90 mg. per 100 ml.

With general treatment he fully recovered in 48 hours and was then able to give a proper history. Three days before admission there had been a very fatty joint of beef for lunch: most of his friends had left the fat on their plates, and he had collected and eaten it all, as "he did not like waste."

It is to be presumed that this large amount of fat, to which he was unaccustomed, produced the ketosis. He stated that he was said to have suffered from acidosis as a small boy.

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Reviews

PATHOLOGY ILLUSTRATED

Color Atlas of Pathology. Prepared under the Auspices of the U.S. Naval Medical School of the National Naval Medical Center, Bethesda, Maryland. (Pp. 546; 1,053 figures on 365 plates. £7.) Philadelphia and London: J. B. Lippincott Company. 1951.

This is a staggering production. It contains well over a thousand photographs in colour, most of which are of histo-pathological subjects and cover a surprisingly wide field. The material used was collected by the Pathology Department of the U.S. Navy, the Pathological Institute of the U.S. Army, the Johns Hopkins Hospital, and the Georgetown University Medical School. Charles F. Geschickter and a group of pathologists serving in the U.S. Navy directed the compilation of the atlas. A team of civilian artists, lithographers, and highly skilled technicians carried out the technical work.

The lesions are classified on a regional basis. Each group of photographs illustrating the diseases affecting a particular organ or tissue is preceded by an introductory text, in which structural changes are clearly described and carefully correlated with their bacteriology and clinical manifestations. A short clinical history and a cytological description of each photograph serves as its legend. Although the book is described as a colour atlas, the inclusion within its covers of a clearly written account of the diseases affecting each system has almost transformed it into a textbook of special pathology.

The colour rendering of the photographs is true, and most of them are superb examples of photographic craftsmanship. The technique is so good that every imperfection in the histological preparation becomes accentuated and every mistake in the selection of the microscope material magnified. Far too many poor preparations have been used, and in far too many sections there is very clear evidence that a blunt knife was used to cut them, that their fixation was delayed or imperfect, or that after staining differentiation was careless and imperfect. In a small but significant number of instances the histological standard of the sections used is so poor that the photomicrograph has little or no value for teaching or comparative purposes. In spite of these imperfections, the number of disease processes adequately illustrated is so large, and so many rarely encountered conditions are included, that the book will be of considerable service to the advanced student and to the practising histo-pathologist.

GEOFFREY HADFIELD.

GROUP THERAPY

Analytic Group Psychotherapy with Children, Adolescents, and Adults. By S. R. Slavson. (Pp. 275. £1 2s. 6d.) New York: Columbia University Press. London: Geoffrey Cumberlege. 1950.

Over fifteen years have passed since attempts were made to extend psychotherapy over a larger field by taking patients in groups and thus dispensing with the difficulty of intensive individual sessions. In Britain the method was described by Bion and Rickman; in the Western Hemisphere much more has been written about it, and the present author has written extensively. Every school of psychiatry now attempts to use the method of group therapy, and included in this wide term must be the work of the Institute of Social Psychiatry, psychodrama, discussion groups specifically intended to be therapeutic and analytical, as well as discussion groups which may have little intention to analyse but believe in a vague way that a gathering of suitable patients for some social activity may itself be successful.

The present volume is written from an extension of the Freudian viewpoint. The author describes two types of group psychotherapy. The first is "active"—what we should describe in this country as play therapy, but clearly intended to make much use of psychoanalytical interpretations to the children. The second is "analytical," and is intended for pubertal or adolescent children as well as adults. Interpretations follow standard lines, and the author asserts that in a group the great difficulties of transference situations are lessened, partly because the attachments of each individual are spread between the relationship to the therapist and to the other group members. He does not emphasize enough that some patients are bad attenders—but perhaps in New York they are not. The author seems to find it easy to choose members of a group who will mix suitably, and the problems of sifting, rejecting, and re-grouping seem to the reviewer to be solved too readily. Indeed, the least satisfactory parts of the book are those which attempt to explain selection.

The part which has interested us is the description of therapy with mothers of difficult children. They are indeed one big factor in children's maladjustment. If successful methods with parents of disturbed children could be found, many obstacles would be lessened. The scornful can find much to criticize and the agnostic to doubt. But we would emphasize that group psychotherapy does require an extended trial, not only to save time in treatment, but to enlighten problems of the group and to tell us more about the failure to socialize which is the hallmark of the psychiatric case—more so, perhaps, than his "Oedipal problem."

Books of this nature should not shut our eyes to other methods of dealing with the mass of psychiatric material which the present age presents. There are a sufficient number of ideas streaming from the descriptions of Freudian methods to stimulate anyone who takes care to read this book.

HENRY WILSON.

HIGHLAND HOSPITAL

The Further History of a Scottish Voluntary Hospital. For the period 1930 to 1948, Prior to Inauguration of National Medical Service in July, 1948. By T. C. Mackenzie, M.D., F.R.C.P.Ed. (Pp. 144. 7s.) Inverness: "Northern Chronicle" Office. 1950.

In this further history of a Scottish voluntary hospital describing the growth of the Royal Northern Infirmary, Inverness, from 1930 to the start of the National Health Service, Dr. T. C. Mackenzie has again succeeded in painting a picture of more than local interest. The rapid expansion of "the key hospital of the Highlands" is shown against the background of the accelerating tempo of social change during the past two decades, illustrated by the impact of local and Government authorities on the activities of what was a purely voluntary effort to provide the best medical service for the people of the northern counties. The success of the "venture in public charity and benevolence" which started in 1797 has been due to the devotion and public spirit of all concerned with the management and work

of the infirmary, but the increasing financial burden and expanding scope of the health services required increasing reliance on departmental grants (not always readily forthcoming), and their consequent disadvantages. In reading of the problems encountered and overcome in the detailed management of a growing voluntary hospital the need for the integration of the hospital services on a regional scale becomes apparent, but it is also clear that the successful administration of an individual hospital, in the interests of the patients and staff, will continue to depend on the personal interest and enthusiasm of those concerned in its local management.

Dr. Mackenzie has rendered a service to all those interested in the history of medical and social development in this country, and his book may be read with advantage by all concerned with hospital management under the new conditions of the National Health Service.

E. A. CORMACK

VECTOR-CARDIOGRAPHY

Études Pratiques de Vectographie. By E. Donzelot, J. B. Milovanovich and H. Kaufmann. (Pp. 253; 118 figures. Paper covers 2,800 francs, cloth covers 3,000 francs.) Paris: L'Expansion Scientifique Française. 1950.

This book on practical studies in vector-cardiography (as we term it here) is well worth study by anyone who wishes to read a clear account of this new method of recording the electrical changes in the heart. Written with the precision and clarity that the French language affords, it is a welcome change from the confused jargon which still further obscures the thoughts of some who write on cardiological matters in our own tongue.

The first chapter gives some geometrical ideas and explains and defines the terms used. There is a clear exposition of how the special vector-cardiogram is obtained from unipolar leads V_2, V_6, and V_F. By these contacts the vectors are studied in the frontal, sagittal, and horizontal planes. It seems odd to find no reference to Lewis in the discussion of the "intrinsic deflection," nor to Wilson in connexion with the "solid angle." In the choice of the polarity of the vectors, the authors regret the lack of agreement between those who use "negative" and "positive" loops. They favour the electronegative, running "north-westerly," rather than the positive (running south-east). They claim that the transition from the ordinary leads is easier so.

There follows a short discussion of the significance of the vector-cardiogram; the conclusion is that the "doublet" theory is untenable. Next comes an analysis of the three loops, P, QRS, and T. Two chapters follow on technical and instrumental details. Then comes a discussion, following Wilson's ideas, of the position of the heart. The authors point out that the loop is the most direct indication of this, and also of rotation round the other axes. Space is too small to say more. There are many pages of clear illustration; on the whole the loops are easy to see, especially when "rolled out." Examples are given—of hypertrophy, infarcts, bundle block, and so forth. It is a new language, but not too hard, and worth looking into. But whether the vector-cardiogram can say in one loop what it takes 12 leads (perhaps) of the cardiogram to express is rather doubtful, yet one feels it says something that cannot be expressed in any other way, and it remains to exploit its clinical application.

TERENCE EAST.

WIDE APPEAL

How I Cured My Duodenal Ulcer. By John Parr. (Pp. 160. 8s. 6d.). London: Michael Joseph. 1951.

The title of this book will appeal to half a million readers, including a great many of the medical profession. The contents consist of the detailed case history of a man with duodenal ulcer who underwent the standard forms of medical treatment and had a laparotomy performed. He continued to have relapses of increasing severity until he was referred to Dr. J.-J. Spira and was recommended a low fat diet. This was five years ago; since then he has had no further symptoms. In addition to the case history, which is entirely classical, the book includes a commentary on the modern view of the pathogenesis of peptic ulcer from the point of view of a layman who has spent many hours in a medical library. Dr. Spira's hypothesis that chronic ulcers are attributable to the local effects of an admixture of bile and hydrochloric acid and that the flow of bile can be kept within safe limits by a low fat diet is, as is natural, given pride of place; the recommended diet is expounded in considerable detail.

The whole book is written in an attractive and readable style and, in the main, is balanced and restrained. The exposition of the bile and acid hypothesis is, however, unconvincing, and Dr. Spira himself will probably be among the first to express dissatisfaction at its publication. There can be no experienced physicians who have not records of patients who could write similar accounts of how they were cured by histidine, by the special formula of a chemist, or even by standard treatment. The test of a treatment for most conditions, particularly for non-fatal relapsing conditions like peptic ulcer, is a controlled trial run on scientific lines, and it is unfortunate that the author is unable to refer to the results of any such trial published by Dr. Spira. If the book stimulates the undertaking of a controlled trial it will have served a useful purpose: no physician can be so satisfied with his present method of treatment that he will not welcome a new suggestion. There is, however, one overwhelming objection to the report of a method of treatment in the form here made—namely, that if the treatment should prove ineffective it will cause bitter disappointment to the many thousands whose hopes are unavailingly aroused.

R. DOLL.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Royal Northern Operative Surgery. By the Surgical Staff of the Royal Northern Hospital. Edited by Sir L. Barrington-Ward, K.C.V.O., M.B., F.R.C.S. 2nd ed. (Pp. 638. 90s.) London: H. K. Lewis. 1951.

First Aid in Coal Mines. By the St. John Ambulance Association. (Pp. 108. 1s. 5½d., post free.) London: St. John Ambulance Association. 1951.

An Introduction to Health Education. Edited by R. Sutherland, M.D., D.P.H. (Pp. 51. 7s. 6d.) London: Central Council for Health Education. 1951.

Poisons: Their Isolation and Identification. By F. Bamford, B.Sc. 3rd ed. (Pp. 316. 25s.) London: J. and A. Churchill. 1951.

Theory of Mental Tests. By Professor H. Gulliksen. (Pp. 486. 48s.) London: Chapman and Hall. 1950.

The Kidney: Medical and Surgical Diseases. By A. C. Allen, M.D. (Pp. 583. $15.) New York: Grune and Stratton. 1951.

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CONTROL OF THE PITUITARY

It is well known that the "conductor of the endocrine orchestra," as the pituitary has been called, can be influenced by his own instrumentalists; it also appears that he can be influenced by his audience. The notion of one gland controlling, as it were by its own initiative, the numerous and varied functions of all the other endocrines has long been abandoned. The output of thyroid-stimulating hormone, for instance, depends on the level of thyroid hormone circulating in the blood, and there are other examples of the activity of the pituitary being modified by the secretions of the glands it stimulates. More recently it has become clear that the hypophysis may also be regulated by nervous impulses which have their origin in stimuli from the outside world, and this neural control of the pituitary is the subject of two lectures by Dr. G. W. Harris published in last week's and this week's *Journal* (pp. 559 and 627).

The subject is full of difficulties for the experimental physiologist. The anatomy of this small and inaccessible but important gland has been obscured by uncertain terminology. Further, the hypophysis is so situated that one standard method of endocrinological research—that of removing the gland and seeing what happens—is difficult to employ efficiently; for if one removes one lobe it is hard to avoid removing the other as well, and even if removal is apparently complete small pieces of secreting tissue may be left behind. It is not surprising that some of the results recorded in the literature are confused and conflicting. Another problem is to detect and estimate the secretions produced by the hypophysis after stimulation. There is no way of doing this chemically, so that the output of hormone has to be gauged by measuring certain bodily reactions in the animal, and if possible matching those reactions by injections of various amounts of standard pituitary extract.

In spite of these difficulties it is now possible to speak confidently about the neural control of the posterior pituitary, or neurohypophysis. Numerous nerve fibres pass from the supraoptic nucleus of the hypothalamus to all parts of the neurohypophysis, where they end in close connexion with the secreting cells, so that it is easy to imagine impulses set up in the nucleus travelling down to the gland and causing it to secrete. That this can happen was shown by Verney, who noticed that water diuresis in dogs could be temporarily inhibited by any emotional stimulus, such as pain, and that this effect of emotion was abolished by cutting the supraoptico-hypophysial tract. Some beautiful work on this problem has been done by Harris himself, using an ingenious technique of his own. He imbeds in the tissues superficial to the skull of a rabbit a small coil connected to an electrode which pierces the bone and passes down so that its tip rests in the supraoptico-hypophysial tract. The rabbit recovers from the operation, and its tract can be stimulated if another coil, connected to an alternating current, is held over its head. When this is done there occurs not only inhibition of diuresis, such as Verney obtained after emotional stimuli in dogs, but also certain other effects characteristic of posterior pituitary activity. One of the most interesting of these is the expulsion of milk from the nipples. Harris finds that if the tract is stimulated drops of milk are forced out of the nipple; if the tract is destroyed, stimulation is ineffective, and moreover the young have difficulty in obtaining the milk from the mother's mammary glands. Work on these lines by Harris and others strongly suggests that the neurohypophysis secretes in response to the stimulation of suckling, and that this galactagogue action (which is quite separate from the lactogenic action of the adenohypophysis) is a true hormonal process and not merely a freak effect of the oxytocic fraction of pituitary (posterior lobe) extract, as was formerly supposed.

The neural control of the adenohypophysis (anterior pituitary) is a more difficult problem. It is well known that certain activities, such as ovulation in the rabbit, which are controlled by the adenohypophysis are affected by nervous stimuli; but it has been difficult to see how these stimuli reach the gland, for in contrast to the neurohypophysis there are no nerve fibres to carry the impulses to the secreting cells. However, stimulation of tracts in the hypothalamus does produce ovulation, whereas stimulation of the gland itself does not. Harris and his colleagues have reinvestigated the anatomy of this region and suggest that nervous impulses reaching endings in the tuber cinereum liberate a chemical substance. This transmitter is then carried by a special system of blood vessels—the hypophysial portal vessels—to the glandular tissue of the adjacent adenohypophysis, where it causes the cells to secrete. If the portal vessels are cut the pathway is interrupted, but the

response to stimulation soon returns, as the vessels quickly regenerate. If, however, a foreign body is inserted to prevent the vessels regenerating the system is put permanently out of order.

The control of the adenohypophysis is of special interest, because A.C.T.H. is liberated in response to the varied forms of stimulus known as stress. Whether stress causes secretion of adrenaline, which in turn stimulates the adenohypophysis, or whether it has a direct stimulating effect, or whether both occur, is not yet settled. Harris suggests that under normal conditions A.C.T.H. liberation is controlled via the hypothalamus and the hypophysial portal system by the level of circulating cortical hormones. Exactly how stress causes secretion of A.C.T.H. is not understood, but it seems likely that the impulses reach the adenohypophysis by the same neurovascular pathway. Some results are conflicting, and it is likely that different species of animal react in different ways. Moreover, the various theories put forward are not mutually exclusive, so that more than one mechanism may be called into play at one time. The subject of stress is now in fashion, and much research is being done on it. If all that research has the same qualities of patience and ingenuity that are apparent in the work of Harris and other authors he cites these problems will soon be solved.

VACCINATION AGAINST SMALLPOX

The Society of Medical Officers of Health have performed a useful service in publishing an authoritative statement[1] on the policy, technique, and materials of smallpox vaccination, a subject on which there is, surprisingly, still much confusion. After reaffirming the society's complete confidence in vaccination as a means of protection of the individual and the community against smallpox if carried out properly and at appropriate intervals, the statement continues with recommendations that primary vaccination in the first six months of infancy should be encouraged to the widest extent; that in non-epidemic periods parents of children who have received primary vaccination in infancy should be urged to have these children vaccinated during school life; and that in non-epidemic periods parents of children who have not received primary vaccination in infancy should not be actively urged to have these children vaccinated for the first time at school entry or later, though vaccination should be carried out if the parents request it. The statement contains definite recommendations on such questions as, for example, the desirability of relying on selective vaccination of contacts in the presence of smallpox—a policy which helps the public to avoid the panic that may be induced by immediate resort to mass vaccination. Among the practical matters dealt with in the section on technique is included a recommendation that the site of vaccination should be covered only when the patient is engaged in some dirty occupation. There is no doubt that dressings tend to create a warm, damp atmosphere encouraging to secondary infection, and that free access to the air usually leads to the formation of a clean dry scab. Contraindications to vaccination are the presence of allergic eczema, septic skin conditions, or acute febrile conditions. "The danger of death following vaccination of those suffering from allergic eczema is so great that they should not be vaccinated."

It is perhaps a pity that some consideration of the duration of immunity after vaccination, the protection afforded by vaccination after contact with smallpox, and the methods of measuring individual immunity were not within the scope of the society's statement, since these are questions uppermost in the minds of many practitioners whenever an outbreak of smallpox occurs. In all immunological problems of this kind there are many individual exceptions to the general rule. Thus, if a group of men or of experimental animals are examined for their individual immunity after any form of preventive inoculation it will be found that there is wide variation in both the degree and duration of the resulting immunity. Although Jenner's original contention that vaccination conferred lifelong complete immunity cannot be maintained, it is probable that it does provide some permanent protection in that a person who has once been successfully vaccinated is less likely to die from smallpox than an unvaccinated person. General epidemiological experience, however, indicates that in order to maintain the immunity of the community at a sufficiently high level the frequency with which revaccination is desirable bears a direct relation to the existence of endemic smallpox in neighbouring countries, for on this is likely to depend the frequency with which infection is introduced. Thus revaccination is recommended at shorter intervals in Japan, Indonesia, and the U.S.S.R. than in most European countries. In 1896 a Royal Commission considered that, in general, immunity lasted for 10 years after successful vaccination, and 30 years later Leake[2] recommended revaccination every 5 to 10 years. To-day it is thought that those who may come into contact with smallpox should be revaccinated after two years, since the immunity of an individual may be much less than that of the community as a whole.

1 *Publ. Hlth, Lond.*, 1951, **64**, 214.
2 *Publ. Hlth Rep., Wash.*, 1927, **42**, 221.
3 *Docum. neerl. indones. Morb. trop.*, 1951, **3**, 163.
4 *Lancet*, 1944, **2**, 697.
5 *Mon. Bull. Minist. Hlth, Lond.*, 1945, **4**, 2.

There has been much discussion about the best way of assessing the duration of immunity. Three methods are available : epidemiological and clinical observation, the cutaneous reaction to revaccination, and the estimation of antibodies in the serum by measuring either its virus-neutralizing potency or its capacity to prevent the agglutination of red blood corpuscles by the virus. The first method has given much useful information about both herd immunity and the protection of the individual, though it has also brought to light startling exceptions to the general rule. The second method, which depends upon observation of the type of skin lesion that results from revaccination, has been generally accepted as a reasonably reliable guide to the immunity of the individual. The reactions are classified as primary non-immune, the "accelerated" (that is, vaccinoid or partially immune), and lastly the more debatable "immediate" reaction, which may or may not indicate a firm immunity. Recently some doubt has been thrown on the reliability of these skin reactions, and the measurement of circulating antibodies has been advocated. Collier[3] in particular has recommended the measurement of the inhibition of virus haemagglutination by the serum, but it is uncertain whether this antibody bears a direct relation to the protection of the individual ; if circulating antibodies are to be measured, the neutralization of virus growth either on the skin or in the chick embryo still seems to be preferable.

Despite individual anomalies, which Stevenson[4,5] reviewed a few years ago, the reaction to revaccination is probably the more direct measure of capacity to react to infection. Although the titre of circulating antibodies may be low, the basic immunity to an antigen that has been encountered in the past enables the body to react rapidly, and this is indicated by the modification of the skin reaction. This is probably the reason why cutaneous immunity can be demonstrated for much longer periods than circulating antibodies. Stevenson concluded that herd immunity lasts for 10 years, but that individual protection is much more variable and may fall far short of this. He pointed out that protection was not dependent on the potency of the lymph, since it resulted equally from vaccination with undiluted lymph or lymph diluted ten-thousandfold. A vesicular "take" is sufficient, but the development of the vesicle may depend upon the idiosyncrasy of the host and not on the quality of the lymph ; this variation exists in many species of animal as well as man. His conclusion that the immunity does not depend upon the dose of virus is relevant to the prolonged controversy over the desirability of multiple insertion of the virus and the relation of area of scarring to duration of immunity. It is not surprising that the immunity developing after the injection of a killed bacterial antigen or a toxoid should have some relation to the dose inoculated, but Jennerian vaccination depends upon the inoculation of a living virus which multiplies in the body of the host. The final concentration of virus bears little relation to the amount originally inserted, and this is why the development of a typical vaccinial vesicle is the all-important indication of successful vaccination.

If called upon to make a dogmatic statement about the protection afforded by vaccination after exposure to smallpox the practitioner can safely say that complete protection may be expected in *most* cases if vaccination takes place within 24 hours of exposure. Some modification of the disease may be expected if the patient is vaccinated within three days of exposure. Beyond that interval vaccination exerts little or no influence on the infection. The protection conferred by vaccination in the early stages of smallpox depends upon the more rapid evolution of the vaccinial infection, but the response of the individual and probably the degree of infection with variola must also have some effect. Thus the protection of vaccination cannot always be absolute.

MUCINOUS SUBSTANCES

In recent years emphasis has been laid upon the importance of localized disturbances in the connective tissues as manifestations of rheumatic and other conditions. Important among the components of these tissues are the mucinous ground substances containing mucopolysaccharides such as hyaluronic acid and chondroitin sulphate. These substances, like the more familiar starch and glycogen, are members of that larger group known as polysaccharides, being polymers of sugar derivatives. Mucopolysaccharides are distinguished from other polysaccharides by containing amines of either glucose or galactose or of both sugars. Hyaluronic acid and chondroitin sulphate also contain an acid derivative of glucose known as glucuronic acid. Other mucinous substances have in their structure a variety of sugars or sugar derivatives as well as the amines of these substances. In some the polysaccharide is closely associated chemically with protein, and it has been claimed that this is true of all mucopolysaccharides.

The history of the study of connective tissues is to some extent being reflected in that of the mucins. Hyaluronic acid and chondroitin sulphate occur in normal tissues as very large molecules and were seen

at first as performing simply structural roles in maintaining the shape and integrity of tissues by absorbing large quantities of water. Indeed, this must be an important function of hyaluronic acid in vitreous humour or in synovial fluid, and of chondroitin-sulphate in hyaline cartilage. Work appearing now, however, suggests that the mucins may have other and more dynamic parts to play—a possibility already displayed by the biological activity of heparin, itself a mucopolysaccharide. There seems, for example, to be a close connexion between the presence of mucopolysaccharides and the formation and maintenance of protein as collagen fibres.[1,2] In the areas of healing skin of experimentally wounded animals mucopolysaccharides appear long before collagen fibres; in scurvy, a condition in which collagen formation is notoriously poor, the mucopolysaccharides fail to appear, or do so in very much smaller amounts and with a different distribution. On feeding the animals with vitamin C, the mucopolysaccharides appear first, followed later by collagen. In ossification again there is a change from a tissue rich in polysaccharides to one rich in collagen; the picture in this instance, of course, is much complicated by the deposition of insoluble calcium salts. Even in fully differentiated tissues collagen fibres appear to be always associated with small amounts of mucopolysaccharide, and it seems reasonable to suggest that these small amounts of material are concerned with the maintenance of the protein fibrils.

In pathological conditions such as rheumatoid arthritis, rheumatic fever, and periarteritis nodosa some change in the local concentrations or quality of mucinous substances occurs. This may be demonstrated by alteration of the viscosity of synovial fluid as is claimed to occur in certain arthritic conditions,[3] or by the local production of mucopolysaccharides around Aschoff nodules and within valvular vegetations as shown by histochemical methods,[4] or as in a variety of pathological conditions by deposition of amyloid in the spleen. Thus it seems reasonable to examine the hypothesis that these conditions represent a disturbance in mucopolysaccharide metabolism with collagen changes as a secondary phenomenon.

It is not only in relation to the so-called connective tissue diseases that ideas for new roles of the mucinous substances are being entertained. In recent years it has been shown that the influenza virus exerts an enzyme-like action upon some component of the surface of the red blood corpuscles in many species of animal[5]; similar mechanisms are probably involved in the adherence of the virus to the bronchial epithelium in an attack of influenza. This sticking of the virus to cells is inhibited by many mucins, including those present in saliva and bronchial sputum, which are likewise enzymatically attacked. Very recently[6,7] the chemical mode of breakdown of one such mucin—that from egg white—has been elucidated. Thus it appears that the balance between defence and attack in the host may be held by the quantity and quality of mucins secreted over the epithelial surfaces of the upper respiratory tract. Evidence is available to suggest that the entry of other viruses into host cells may also involve mucinous substances.

It can be seen that there is considerable incentive to extend our somewhat meagre knowledge of the metabolism and nature of the mucins. There is already strong evidence in favour of hormonal and nutritional control of their production. For example, mucopolysaccharide formation in the sex skin of monkeys and in the comb of the cockerel is controlled by oestrogens and androgens; the evidence for the role of vitamin C has already been mentioned. Beyond this, however, we have very little knowledge. It has been suggested that building units for hyaluronic acid may be formed in the liver and polymerized locally to the full mucopolysaccharide, but the evidence for this is not particularly good, and as a general theory for the formation of mucins would scarcely seem to be satisfactory. Quite apart from this more complicated problem of the metabolism of these substances there is the need for further knowledge of the chemistry and physiology of the substances present in mucinous fluids such as sputum or saliva, or in the nasal and prostate secretions. It seems that an important chapter in biochemistry is likely to be written on the mucins during the coming years.

1 Penney, J. R., and Balfour, B. M., *J. Path. Bact.*, 1951, **61**, 171.
2 Bradfield, J. R. G., and Kodicek, E., *Proc. Biochem. Soc.*, 1951, in press.
3 Meyer, K., *Physiol. Rev.*, 1947, **27**, 335.
4 Altschuler, C. H., and Angerine, D. M., *Amer. J. Path.*, 1949, **25**, 1061.
5 Burnet, F. M., *Physiol. Rev.*, 1951, **31**, 131.
6 Gottschalk, A., and Lind, P. E., *Nature, Lond.*, 1949, **164**, 232.
7 —— Ibid., 1951, **167**, 845.

PROGESTERONE AND ECLAMPSIA

The possibility that late pregnancy toxaemia is a manifestation of hormonal imbalance has occurred to many, though it is to the Smiths[1] that we owe the most extensive investigations and the most elaborate hypotheses. They consider that the hormone pattern characteristic of this condition consists of increased chorionic gonadotrophin with decreased oestrogen and progesterone levels in the blood. Inadequate "hormonal support" of the placenta leads to the production of a substance similar to "menstrual toxin," which in turn is responsible for most of the clinical characteristics of the disease. Opinions, in this country at least, are divided on the views put forward by the Smiths, but though recent work[2,3] does not support all their claims—for instance,

that chorionic gonadotrophin is always increased, that pregnanediol excretion is diminished, and that administration of oestrogens causes a return to normal of these values—it must be admitted that much of their most important work has never been repeated by other investigators.

In order to gain further insight into the disease several workers have attempted to induce a corresponding condition in experimental animals. Nothing relevant is to be learned from the effects of posterior lobe extracts, since it is generally agreed that no condition resembling late pregnancy toxaemia in humans results from their administration. Green,[4] however, observed eclampsia-like lesions in pregnant rabbits after giving aqueous extracts of ox anterior-pituitary gland (often rich in luteinizing hormone) and of chorionic gonadotrophin (also mainly luteinizing in action). Previous attempts to demonstrate eclamptogenic effects with progesterone[5 6] had failed, but more recently Symeonidis[7] has reported notable results from the administration of 5 mg. daily of progesterone to rats during the last third of pregnancy. Death, abortion, or resorption of the embryo, as well as obvious illness and death of the mothers, were consequences of this treatment. This author found albuminuria, azotaemia, oedema, and hypertension in the experimental animals, together with lesions in various organs, particularly the liver and kidneys, closely resembling those of human late pregnancy toxaemia. In the liver peripheral lobular necrosis was present, with capillary dilatation, fibrin thrombi, and haemorrhages; and in the kidneys fibrin thrombi in glomeruli, thickening of the glomerular basement membrane, and tubular degeneration and necrosis. Another feature resembling the human disease was the recovery of some of the treated pregnant rats after they had given birth to dead embryos and damaged placentae—an argument for the supposition that progesterone injured the embryos and placentae, with the consequent elaboration of toxic substances. On the other hand, the same treatment given to pregnant rats before the last third of pregnancy or to non-pregnant rats failed to have any comparable effects.

It seems difficult to reconcile these findings with the views put forward by the Smiths, and with Priscilla White's[8] advocacy of the use of progesterone in the treatment of pregnant diabetics (who have a greatly increased incidence of late pregnancy toxaemia) with the object of preventing the occurrence of toxaemia. Two possibilities, however, should be considered before attaching either too great or too little importance to Symeonidis's findings. The first is that the doses of progesterone he used were so great as to produce a toxic effect of their own (which seems unlikely, in so far as they did not harm non-pregnant rats or rats in the early stages of pregnancy); and the second is that the conditions obtaining in rats bear no strict comparison with those in the human. On the whole, too little attention is paid to this possibility, there being all too often an undue readiness to accept the results obtained with one species as applicable without reservations to another.

[1] Smith, G. van S., and Smith, O. W., *Physiol. Rev.*, 1948, **28**, 1.
[2] Sommerville, I. F., Marrian, G. F., and Clayton, B. E., *Lancet*, 1949, **1**, 680.
[3] Loraine, J. A., *British Medical Journal*, 1949, **2**, 1496.
[4] *J. exp. Med.*, 1937, **65**, 809.
[5] Dexter, C., and Weiss, S., *et al.*, *Pre-eclamptic and Eclamptic Toxaemia of Pregnancy*, 1941, Boston.
[6] Selye, H., Stone, H., Nielson, K., and Leblond, C. P., *Canad. med. Ass. J.*, 1945, **52**, 571.
[7] *J. nat. Cancer Inst.*, 1949, **10**, 711.
[8] *Penn. med. J.*, 1947, **50**, 705.

CHEMOTHERAPY OF FILARIASIS

Until a few years ago the treatment of filariasis was succinctly summed up in Belloc's words—"There is no cure for this disease." In 1945 Cuthbertson and Rose[1] showed that antimonials such as "neostibasan" killed the adult filariae, if given in subtoxic doses, and Otto and Maren[2] later showed that arsenical compounds such as "arsenamide" could achieve the same result. Welch and his collaborators[3] described a cyanide compound (No. 863) which was very promising in experiments on infected cotton-rats; unfortunately it was unsuccessful in man. The only compound which has been really successful in clinical practice is the piperazine derivative known as "hetrazan" or "banocide," which was announced by Hewitt and his collaborators in 1947.[4]

Hetrazan produces its antifilarial action in a remarkable manner.[5] Its main chemical effect is on the microfilariae rather than on the adult worms, although it has no action upon microfilariae *in vitro*. Normally these young worms are so well adapted to existence in their host that they circulate in the blood without causing any bodily reaction. But hetrazan somehow modifies them so that they become recognized as foreign bodies by the phagocytic reticulo-endothelial cells of the liver, which filter them off and subsequently destroy them. Thus hetrazan acts like an artificial "opsonin," which "butters" the microfilariae, and they vanish from the circulation almost instantaneously.

Against adult worms hetrazan is not quite so active, the degree varying with the species concerned. Against the adult worms of *Onchocerca* its action is slight. Against the adult worms of *Loa* it is more effective, and one or more 10-day courses of hetrazan, given as 2 mg. per kg. thrice daily, is usually enough to cure this non-fatal but troublesome infection. In the case of *W. bancrofti*, which is the most important type of filarial infection, the position is not quite clear, since it is impossible to make direct observations on the adult worms, which live deep in the lymphatics. Since, however, the microfilariae disappear from the blood when an adequate course of hetrazan is given, and do not reappear even after 12 months, it is possible that hetrazan is effective in killing the adult worms of this infection; it at least prevents them from reproducing.

Hetrazan is a non-toxic compound, and in patients without filariasis it can be given in doses as great as

[1] *Trans. roy. soc. trop. Med. Hyg.*, 1947, **41**, 18.
[2] *Amer. J. Hyg.*, 1949, **50**, 92.
[3] *Science*, 1947, **105**, 486.
[4] Santiago-Stevenson, D., Oliver-González, J., and Hewitt, R. I., *J. Amer. med. Ass.*, 1947, **135**, 708.
[5] Hawking, F., *Trans. roy. Soc. trop. Med. Hyg.*, 1950, **44**, 153.

10 mg. base per kg. without producing any untoward effects worse than a little nausea. When, however, it is given to patients with onchocerciasis (in which condition there are many young worms in the skin) or to cases with heavy infections of *W. bancrofti*, it may provoke febrile reactions, generalized itching and inflammation of the skin, and tenderness and swelling of the lymph glands. Apparently these reactions are allergic in nature, being due to the liberation of chemical products from the microfilariae in persons who have become sensitized to them. The reactions subside in a few days, after which higher doses can be given with impunity.

The uses of hetrazan are not yet fully explored, but the drug will probably be very useful for the cure of Europeans and similar persons infected with *Loa*. It may be useful in patients infected with *Onchocerca*, in whom the microfilariae are causing troublesome symptoms, such as disturbance of vision, but it will not remove the ultimate infection—i.e., adult worms. In the treatment of *W. bancrofti* it will remove the microfilariae and will probably kill the adult worms. Owing, however, to the peculiar nature of this infection most of the people who carry microfilariae suffer no disability and will therefore not put up with much trouble or discomfort to get rid of the worms; yet these are the people whom it is most important to treat, for some of them will ultimately develop elephantiasis, and all of them constitute a reservoir of infection from which the disease is transmitted to others. At this point the tendency of hetrazan to produce mild nausea becomes very important, for it would be sufficient to render it unpopular and unacceptable if handed out in mass-campaigns in an attempt to suppress or eradicate filariasis. Accordingly it is doubtful whether hetrazan will really be so effective for the complete eradication of filariasis by mass-treatment as was initially hoped.

ERGOTISM

Attacks of ergot poisoning are so rare to-day that few people have ever seen a case. The standard textbooks differ somewhat in the accounts they give of the clinical picture, and in view of the complexity of ergot it is probable that the emphasis of the symptoms will fall differently on different occasions, depending on the ratios of the different toxic principles present. Three active alkaloids and a number of bases such as histamine and tyramine have been recognized in the whole extract; and while, for instance, ergotoxine and ergotamine are poorly and irregularly absorbed from the intestine, ergometrine very quickly enters the circulation, and its pharmacological effects are also different.

The clinical report on page 650 of the recent outbreak at Pont St. Esprit is therefore particularly valuable. The nausea, vomiting, and diarrhoea of many cases, the weak pulse, and bradycardia are all well-established indications of alkaloidal poisoning, as are the peripheral signs of vascular injury, pallor, and coldness of the extremities—and the formication, paraesthesia, and muscular cramps. The burning sensation throughout the intestinal tract, and particularly at the anus, the abdominal pains, the abundant sweating, and the disagreeable odour of the patients were probably due to some of the amine bases present.

But the most unusual feature of the outbreak was the pronounced cerebral symptoms: insomnia preceding restlessness and excitement, and visual hallucinations often followed by dreamy delirium with systematized delusions. It has been suggested in the past that mental symptoms would occur only in the malnourished, who perhaps were lacking in vitamins, but in view of what has recently been learned about "agene," for instance, it seems possible that there may be hitherto unrecognized simple amino-acid derivatives present in ergot and capable of affecting brain function.

The prognosis of the acute poisoning attack appears to be good, and only one case of moist gangrene is so far reported. It is said[1] that atropine can be used to counteract the alkaloidal poisoning, and sedatives presumably are valuable for the mental symptoms. The outlook is worst for those with liver damage, such as the chronic alcoholics. The final report in some months' time should have new light to shed on many aspects of this unusual form of food-poisoning.

[1] Goodman, L., and Gilman, A., *The Pharmacological Basis of Therapeutics*, p. 658, New York, 1940.

ACTION OF DRUGS ON RESPIRATION

In the opening pages of this issue we publish a lecture by Professor G. Liljestrand, of Stockholm, on the action of drugs on respiration. For those working on the clinical aspects of respiration the exposition of the discoveries made in the last 25 years should be of great value, particularly the analysis of the action of respiratory stimulants such as lobeline and of poisons such as cyanide. The consideration of the effects of adrenaline and of acetylcholine also provides an illuminating expansion of the ordinary textbook description of the respiratory mechanism. The study of respiration occupied a great part of British physiology in the period before the first world war, under the leadership of Haldane, Douglas, and Priestley in Oxford and of Barcroft in Cambridge. More recently the main advances have been made in other countries, by Heymans in Belgium, by Schmidt in the United States, and by Professor Liljestrand in Sweden. The last-named gives in the lecture an amusing example of the reluctance with which new work from other countries is accepted by those who have made important contributions themselves: he quotes Haldane and Priestley as saying in 1935 "that the reflex control of breathing by chemical stimulation of the carotid nerve endings has not been established."

Professor Liljestrand has been for many years the secretary of the committee which has awarded the Nobel prizes in medicine and physiology. It will be evident to a reader of the lecture that the holder of that important position is a man of scientific modesty and impartiality who has performed a notable service not only to his own country but to medical science everywhere.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

SUICIDE, ACCIDENT, OR MURDER?

BY

KEITH SIMPSON, M.D.

Reader in Forensic Medicine to the University of London, at Guy's Hospital

When a doctor is called to see an apparently dead body he is being asked to make several decisions, each of which will set in motion (or may restrain) a series of important consequences. He would be wise to remind himself of the mischief—if not grave injustice and danger to liberty—that may follow from carelessness or ignorance in coming to any decision he makes on a "dead body."

Dead or Alive?

The doctor has first to assure himself that death has, in fact, taken place, and though no doubt about this may arise in most cases—indeed the body may be mummified or dismembered—it is essential that he should actually examine the body to assure himself of the fact; it is not enough to assume death. Not long ago a woman whose cold stiff body had been found exposed on a common was certified dead, as she lay under blankets in an ambulance, by a doctor who contented himself with putting a hand on the skin. She was taken to the mortuary, stripped, and placed on the table for necropsy, where she was shortly after seen to be swallowing and undoubtedly also breathing: she survived some seven or eight hours in hospital. Extreme cold, grave loss of blood and shock, vagal inhibition as from immersion in cold water, and electrocution may all simulate death so closely that great care is necessary to avoid this shocking error.

Stethoscopic examination for the heart sounds is the only really reliable test: if there is no heart beat for four or five minutes eventual survival is impossible. Groping with throbbing fingers for a thready pulse can be deceptive, and testing for the breath with a feather or a cold mirror are pantomimic gestures that can only waste vital time. If the doctor is in doubt, or there is difficulty because of noise of traffic or other inconvenience, he should certainly institute resuscitative measures and then have the body removed to a place where it can be examined under better conditions. Resuscitation should not be relaxed until no possible hope of survival exists: striking recoveries have ensued after long periods of apparently suspended animation in cases of electrocution.

How Long Dead?

As a corollary to this first decision the doctor may be asked how long ago death took place. No more difficult medico-legal task has ever existed, and no doctor can do more than give an approximate time. The temperature of the body is a useful guide in the first 24 hours, and this simple test of cooling should not be forgotten, even if the body feels cold, as it may be some 10 to 12 hours before it is actually as cold as its surroundings. For this purpose skin temperatures are unsuitable, and the thermometer should be inserted into either the rectum or a hole made in the abdomen. Some 2° F. (1.1° C.) an hour is the normal rate of loss for a body in the open air in average English weather, but less than 1° F. (0.55° C.) an hour may be lost in bed or when heavily clothed, and as much as 3 to 4° F. (1.7 to 2.2° C.) an hour in cold water: the circumstances will plainly affect the rate of heat loss.

Rigor mortis is an uncertain guide but should, of course, be assessed, as it carries the time limit set by cooling from about 24 hours to about 36. The working rule that rigor, starting in the face at six hours, is complete to the feet and hands at 12 hours, stays for 12 hours, and takes a third 12 hours to pass away is a fair general guide. Rigor is, however, too uncertain to be safe. After 36 hours the basis of estimation—the development of decomposition and its spread into the body from the flanks of the abdomen—goes on slowly and with many vagaries, depending on the initial bacteriology of the bowel, and is largely controlled by climatic conditions. Cold water doubles the rate of cooling and delays rigor and decomposition to the same degree.

Certification or Coroner?

If a doctor has been in attendance during the last illness—preferably within 14 days—and knows the cause of death he has a statutory duty to issue a certificate of death for the registrar.

If he has not attended during the last illness, or if he has any doubts about the cause of death or knows (or suspects) it to be unnatural or associated with injury or violence of any kind (or date), he will only obstruct the public interests by issuing some kind of certificate which will take vital time to pass through the hands of the registrar before being referred to the coroner for inquiry. Where suspicion of crime arises, however faint the scent of foul play, the doctor should, of course, lose no time in informing the police (who may be left to inform the coroner) so that their C.I.D. inquiries may start without delay. A doctor is not compelled by any regulation to report cases to the coroner—the registrar is the official sorter—but only harm can come of deliberately trying to avoid inquiry: obstructing the coroner in the discharge of his duties is, in fact, punishable by imprisonment or fine (or both).

The classes of cases to be referred to the coroner consist, from the practitioner's point of view, of:

1. *Deaths the causes of which are unknown or uncertain*—all cases seen only after death.

2. *Violent or unnatural deaths*, or deaths which might, from the doctor's knowledge, be related to: (*a*) accident or injury of any date; (*b*) want, exposure, or neglect; (*c*) poisoning—by drugs or poisons of any kind; (*d*) abortions if in any way suspicious, and suspicious infant deaths; and (*e*) industrial hazards, including anthrax.

3. *Deaths before full recovery from anaesthesia* or suspected to be connected with operative or other treatment.

Crime or Accident?

The last duty of a doctor confronted with a dead body is to decide, using his training in medico-legal matters,

whether there is any cause for suspicion of suicide or foul play, or whether circumstances and any injuries that may be seen are capable of some simple natural explanation.

It is, of course, no part of a doctor's duty to be a detective, and he must on no account interfere with the setting of a scene which the police may later have reason to examine with meticulous care, to photograph, and to search for fingerprints. He should therefore tread warily and avoid touching anything smooth that might carry prints. A doctor can ascertain the fact of death, insert a thermometer (registering to zero) either into the rectum or into a hole made in the abdomen, and observe superficial injuries, loss of blood, smell or stains of poison, signs of asphyxia, and so on without disturbing the body. He should not let the body be moved if there is any reason for uncertainty, far less real suspicion; he must, however, not fail to make a reasonably painstaking examination before deciding this point.

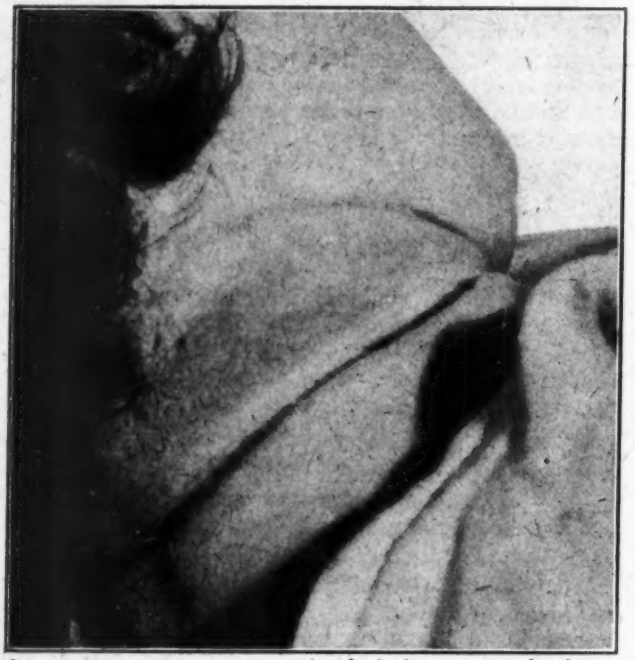


FIG. 1.—Marks on neck, indicating foul play, not seen by doctor called to examine dead girl.

A doctor, called to a house to see the dead body of a girl in bed, looked into the room and saw she lay there covered by the bed-linen up to the mid-neck. He did nothing more, but later informed the coroner of a "sudden death" unattended by him in life. On the coroner's officer making his routine visit for inquiry and turning down the sheets it was evident that the girl had been strangled (Fig. 1). Her mother was found, upon search of the house, under the stairs, also strangled. Valuable time had been lost in a murder hunt.

FIG. 2.—Tentative incised wounds of the throat of suicidal character, inflicted with safety-razor blade.

The recognition of grounds for suspicion, apart from the plainest pedestrian circumstances of murder, rests largely with the doctor's ability to recognize suicide when he sees it. The classical suicidal cut throat, with its tentative incisions (Fig. 2), elective site, curve, and slope; the solitary or doubled stab over the heart, without "protective" wounds to the hands; the contact discharge of a firearm in one of the elective suicidal sites—centre brow (Fig. 3), temple, roof of the mouth, or over the heart—these are all traditional suicidal events that the doctor has been trained to recognize instantly. He may also recognize the suicidal nature of a cut throat which is done with the help of a mirror, the significant grasping of a weapon by cadaveric spasm as it was at the moment of death, and the careful preparation of a coal-gas suicide to prevent ventilation — the circumstantial features that may support his medical findings. He is entitled to use these things to help him evaluate a case.

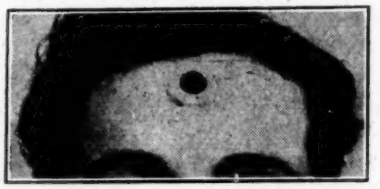


FIG. 3.—Typical suicidal firearm entry wound—a contact discharge set in one of the "elective" sites. A .32 revolver was lying near the right hand.

It is when these classical suicidal features are absent—when the throat wound does not follow the rules or is accompanied by protective hand wounds, when the firearm wound is in an inaccessible part of the body (Fig. 4), or where there is some similar cause for uncertainty—that the doctor must go cautiously. Perhaps some accident is responsible, but only careful inquiry can decide such things, and this inquiry is outside the doctor's province.

When the medical findings are equivocal a doctor is entitled to know what the circumstances were, for special alternative explanations of some wound may exist. A man with a blunt head wound may have had some machinery fall on him or have been thrown pitching on to the head, or have been struck with some blunt weapon: it *is* important to know whether he was working on the docks among loading gear or lying in bed at home. A doctor should certainly obtain all the relevant information he can when injuries of an equivocal kind are present.

A man last seen in loud argument with fellow workers at the entrance to the factory was found dead in the same spot on the ground, alone, about one and a half hours later. He had a head wound (Fig. 5) which could have resulted from a vicious kick from the toe of a boot, but examination of a projecting piece of ornamental stonework at the gate showed some frag-

FIG. 4.—Typical homicidal firearm wound set behind left ear. No weapon at scene.

ments of cuticle and several head hairs identical with the dead man's. He had marked coronary atheroma, and it was realized that if he were to collapse from this (after heated argument) he could well have sustained the otherwise suspicious head wound which he bore.

The full facts are often enough to throw an entirely new light on the medical observations, often to dissipate suspicion, and a doctor need never hesitate to ask what is known so far in order to form a more definite opinion. It is remarkable how much more one sees of a case when it is ultimately argued between opposing counsel before judge and jury at a trial—a trial of possibilities. Every doctor should have an alert and open mind not readily given to always accepting the first obvious explanation of an event, though not, at the same time, stubbornly refusing to accept a reasonable possibility. Medical evidence should always be carefully reasoned and, therefore, reasonable.

Deaths from grave injuries by the roadside should not arouse suspicion until the possibility of a vehicular street

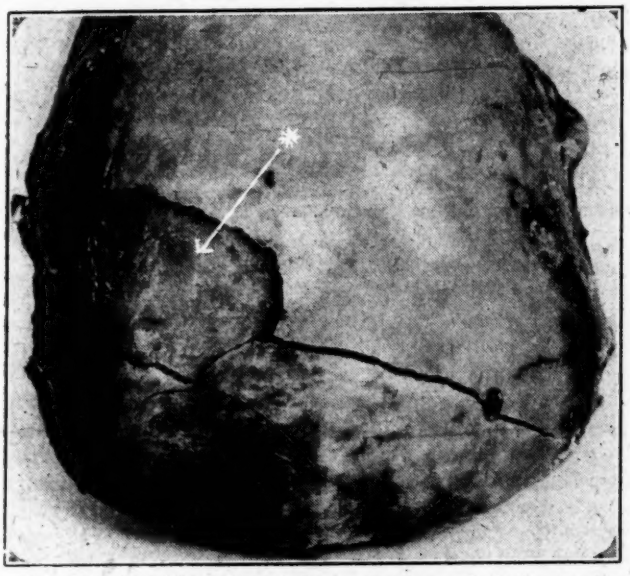


FIG. 5.—Suspicious head injury. Fracture of skull, showing significant shaping of depressed area*. Suspicion of foul play was allayed by revisiting the scene.

accident has been altogether excluded. Bodies found dead in a busy river may be expected to bear injuries sustained after death from passing craft, crabs, or recovery gear. The mutilated victim found in the yard of a block of flats is as likely to have fallen from a higher floor or the roof as to have been "beaten up." The suffocated body lying face down in the pillow is not unlikely to be that of an epileptic, and infants quite often meet their death as a result of turning their faces into the bedding: their position and deep asphyxial coloration need not arouse suspicion of foul play, though it would be wise never to overlook the possibility. Perhaps the only common error in interpreting the facts is to regard the trussed schoolboy, sometimes found hanging only partly dressed, as a suicide: his is undoubtedly an accidental death during a masochistic session.

The doctor who carefully assesses the fact of death, indicates approximately how long ago it occurred, offers a reasonable explanation of the medical findings, and encourages caution in disturbing things unless he is satisfied foul play can be excluded will not expose himself to abuse or ridicule in court, nor will he be likely to commit significant error. Crime and suicide must be recognized without delay, and the doctor's elementary forensic training, together with common sense, will not often let him down in these matters. Where accident seems likely or the position is equivocal a cautious sifting of possibilities *pari passu* with the police inquiry is more likely to achieve the correct solution and to avoid wrecking the scene.

EPIDEMIC SMALLPOX IN JIDDAH

TREATMENT WITH ANTIBIOTICS

BY

N. L. CORKILL, M.D.

Formerly Quarantine Expert, Saudi Arabia

In October, 1949, during the closing days of the Mecca Pilgrimage, it became clear that smallpox was occurring in Mecca, Jiddah, and perhaps Medina, three towns visited by most foreign pilgrims, all of whom, it may be noted, are required to be immunized against smallpox and cholera. Epidemic form was assumed in Mecca and Jiddah, and even as late as the end of May, 1950, a few cases were still coming to light. The disease is known to have been carried by pilgrims to at least Egypt, the Sudan, Pakistan, and India.

In Jiddah particular interest centred on some 1,800 Filipinos who journeyed to and from the Hedjaz in the pilgrim ship s.s. *Christobal*, and among whom smallpox made its appearance first in Mecca. They brought cases with them on their return to Jiddah for re-embarkation. The majority, some 1,300, were revaccinated in Jiddah—as it turned out, not very effectively—and quarantined in overcrowded accommodation on the island of Abu Saad, off Jiddah. The remainder, some 500, evaded quarantine and revaccination and remained dispersed in agents' houses in the town. Those of all races sick from smallpox and coming to notice were admitted to hospital on the remoter island of Wasita. These Filipinos lost about 8% of their number in the Hedjaz, mostly from smallpox, at least 16% of them suffering from the disease.

Among the 500 Filipinos remaining in Jiddah town there was a sharp epidemic of concealed cases, and it seems that through breaking of quarantine the disease was carried, ironically enough, from these people not in quarantine to their brothers in quarantine on Abu Saad island in conditions ideal for the spread of an epidemic in which both contagion and air-borne infection are factors. Mass revaccination of the Abu Saad community was done again with vaccine known to be potent, and the epidemic closed within the incubation period.

In Jiddah itself, though general vaccination was ordered early, it was extremely slow in getting under way, with the result that the recorded cases—there were many unrecorded—were still rising in incidence long after cases among the Filipinos had ceased. It is thought that altogether in Jiddah there were about 1,000 cases in all races, of whom some 58% died. Most cases were in unvaccinated Saudi Arabians.

Control difficulties were great. Too many authorities were involved for efficiency and speed to be reasonably served. Procedure, staff, accommodation, equipment, supplies, drugs, disinfection apparatus, transport, and petrol were inadequate. There was, in short, general unpreparedness. The islands of Abu Saad and Wasita were shown to be unacceptable as quarantine and

isolation hospital accommodation respectively, because of their limitations in size, buildings and fittings, and approachability in bad weather and after dark. Ultimately a tented quarantine camp and an isolation hospital were erected in the desert south of Jiddah to serve until new installations of a permanent type were erected in the near-by desert.

Two major aspects of sanitation demanded attention —flies and disinfection. Flies on the islands and in the desert camp were very effectively banished by blowing a thin film of dust of "gammexane 0.34" anti-fly powder over the floors and ground from time to time with French's bellows blower, choosing windless days. Disinfection of infected houses and their contents was not achieved. All Filipinos with their effects were disinfected to a considerable extent before re-embarkation. For the terminal disinfection of the pilgrims before re-embarkation clothes and bedding were steam-disinfected in two Serbian barrels made from 40-gallon (182-litre) drums, steam being from an oil-fired portable boiler. This equipment was arranged by a local construction company. Papers, leather, and fine fabrics were put through a "bacterol" portable disinfector producing nascent formaldehyde; this procedure, though tedious, was presumed to be efficient enough to be useful. Much use was also made of exposure of kit to the midday sun in the hope that irradiation would destroy residual infection.

The quality of the statistics obtained was poor, but those produced here are sufficiently near the truth to illustrate the nature of events.

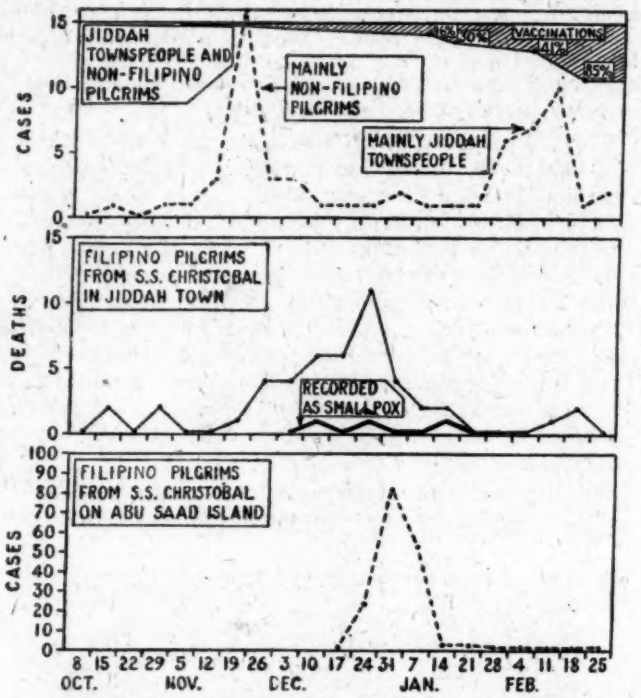


FIG. 1.—Incidence of smallpox in Jiddah as suggested by certain figures. The upper two graphs are based on figures from Jiddah Hospital. All figures are considered incomplete. Vaccinations and revaccinations shown cumulatively.

Epidemiology

Fig. 1 shows that smallpox started in Jiddah in October and assumed epidemic form in November, with a peak in that month formed mainly by non-Filipino pilgrims presumably infected in either Mecca or Medina, and coinciding with the return of the mass of the *Christobal* pilgrims from Mecca, already infected with the disease. Among the 500 Filipino pilgrims who evaded quarantine and revaccination there now began an epidemic of "deaths" recorded under various causes as a necessary preliminary to the issue of burial permits—for example, "fever," "pneumonia," and "unknown"—but without doubt largely smallpox. The number of cases was estimated to be 120, and deaths 40. The peak of this epidemic preceded by a week the peak of an epidemic of smallpox (180 cases and 65 deaths) among the 1,300-odd Filipinos quarantined on Abu Saad after revaccination in Jiddah. The time relationship of these two epidemics in the *Christobal* Filipinos suggests clearly that, if intercommunication existed, then the disease was carried from Jiddah to Abu Saad. In fact, it is known that quarantine was poorly honoured and that intercommunication between the two Filipino communities was frequent.

Conditions on Abu Saad were extremely favourable to the spread of epidemic disease. There were gross overcrowding, climatic rigour due to wind, rain, and

TABLE I.—*Jiddah, 1949–50. Morbidity and Mortality from Smallpox among non-Filipinos. Indirect Statistics (those Calculated on Grounds of Probability) are in Parentheses*

Place	Period	Record	Smallpox Records		Remarks
			Cases	Deaths	
Jiddah town	Oct. 8 to Feb. 25	Registered admissions to Jiddah Hospital for smallpox	63	53	Probably mostly before December 24. There may be some overlapping with the Wasita records, as it was only in October that Jiddah Hospital actually treated cases
Jiddah town	Oct. 8 to Feb. 25	Registered deaths occurring outside Jiddah Hospital, recorded as smallpox	(86)	43	They include women and children
Jiddah town	Oct. 8 to Feb. 25	Registered deaths occurring outside Jiddah Hospital recorded as "fever" and "malaria"	(425)	(213)	Of about 425 entries, about half—including many women and children—showed the cause of death as "fever" or "malaria" As such an incidence of malaria is unacceptable* they may be fairly ascribed to smallpox, and, as it is reasonable to allow a 50% mortality, double the number represents the cases
Wasita island	Jan. 7 to Feb. 25	Clinical records and daily record (N.L.C.)	88	32†	The series is composed almost entirely of casual labour from the market in unvaccinated males from Farasan and Gizzan, who had been living in Jiddah for months or years. There were only two females in the series
Desert camp	Feb. 25 onwards		Epidemic closing		
Total	Oct. 8 to Feb. 25	—	(662)	(321) 48%	

* Between October 1 and February 28, in Jiddah Laboratory, 237 blood examinations were done, and in no blood films from Jiddah residents were malarial parasites found. Endemic malaria rarely occurs in Jiddah.

† One death from drowning is excluded and five record cards were missing.

TABLE II.—*Jiddah, 1949–50. Treatment of Smallpox with Antibiotics in Vaccinated and Unvaccinated Arabians**

Type of Disease and Vaccination State	No.	Deaths and Fatality Rate	Corneal Lesions and Arthritis	Duration of Illness in Days Before		Average Total Dosage§ in Recoveries	
				Death	Recovery	Penicillin (million units)	Streptomycin (g.)
Confluent :							
Vaccinated	6	2	0	11	33	7·2	12
Unvaccinated	17	10 (58%)	0	8	28	6·6	11
Severe:							
Vaccinated	7	4	0	7	31	7·8	11
Unvaccinated	35	16 (45%)	1 (corneal)	6	25	7·2‡	12‡
Moderate :							
Vaccinated	7	0	0	—	18	6·6	11
Unvaccinated	7†	0	0	—	20	6·6	11
Mild :							
Vaccinated	4	0	0	—	10	3·6	6
Unvaccinated	—	—	—	—	—		
Totals :							
Vaccinated	24	6 (25%)	0	8	21	6·2	10
Unvaccinated	59	26 (44%)	1 (corneal)	7	24	6·9	11
Overall total	83	32 (39%)	1 (corneal)	7	23	6·6	11

* Being all cases in which clinical records were available on March 31, 1950. There were three fatal cases of haemorrhagic type.
† One drowned in delirium is excluded.
‡ One treated with aureomycin is excluded.
§ Penicillin, 600,000 units, and streptomycin, 1 g., daily; children half, infants quarter the amount.

TABLE III.—*Jiddah, 1949–50. Treatment of Smallpox with Antibiotics in Revaccinated and Vaccinated Filipino Pilgrims†*

Type of Disease and Vaccination State	No.	Deaths and Fatality Rate	Corneal Lesions and Arthritis	Duration of Illness in Days Before		Average Total Dosage‡ in Recoveries	
				Death	Discharge§	Penicillin (million units)	Streptomycin (g.)
Confluent:							
Revaccinated	11	7	0	9	22	4·8	8
Unrevaccinated	3	1	0	10	18	4·8	8
Severe:							
Revaccinated	41	6 (14%)	2 (corneal)	7	15	3·6	6
Unrevaccinated	4‖	2	1 (elbow joints)	8	16	5·4	9
Moderate :							
Revaccinated	30	0	1 (elbow joints)	—	14	2·4	4
Unrevaccinated	5	0		—	13	3·0	5
Mild :							
Revaccinated	38	0	0	—	12	1·2	1
Unrevaccinated	3	0	0	—	10	2·4	4
Total :							
Revaccinated	120¶	13 (11%)	3	8	14	2·4	3·7
Unrevaccinated	15	3 (20%)	1	8	13	2·5	5·6
Overall total	135	16 (12%)	4	8	14	2·4	3·8

* Revaccination refers only to that done on the island of Abu Saad and known on epidemiological grounds to have been effective.
† Being all cases in which clinical records were available on February 25, 1950. There were no cases of haemorrhagic type.
‡ Penicillin, 600,000 units, and streptomycin, 1 g.; children half, infants quarter amount.
§ Unnaturally high, as many stayed on to look after sick friends and relatives.
‖ One aged 4 refused injections and survived.
¶ Practically all these were incubating the disease when revaccinated.

cold, shortage of food for many, and the vicious circle, only too common in such circumstances, of (*a*) deficiency disease (mainly beriberi and hyporiboflavinosis), (*b*) dysentery and diarrhoea, and (*c*) fly infestation. A sudden crop of 15 cases on Abu Saad led to immediate mass revaccination for the second time with vaccine of proved value. The epidemic closed in 14 days. Factors favouring these Abu Saad Filipinos were a robust physique and previous vaccination experience.

The epidemic among Jiddah townspeople, as suggested by the recorded cases, came to a peak in February (Table I). General vaccination, though ordered on October 29, had crept forward with painful slowness. Other adverse factors were apparent shortage of potent vaccine, ineffectual vaccination, inefficient notification of cases, no vaccination or segregation of contacts, no disinfection of infected houses and effects, cold weather, and public apathy. On the credit side may be put general vaccination, albeit slow, vaccination of new arrivals to some degree, and perhaps stock experience of the disease.

The method of vaccination used in the clearly successful revaccination on Abu Saad was the multiple-pressure method of Leake, the arm being cleaned with soap (a little) and water. No bad reactions were seen apart from one case of generalized vaccinia inevitably diagnosed initially as smallpox, and several reactions of primary type in Filipinos dying of smallpox, and who may have evaded previous vaccination or washed their arms after its being done, and were well on in the incubation period when revaccinated for the second time.

Treatment

In view of the observations of Johnstone and Fluker (1949), once it was possible to organize their administration, procaine penicillin G with aluminium monostearate, 600,000 units once daily, and streptomycin, 0.5 g. twice daily, were given until the lesions were dry, streptomycin being discontinued on the advent of severe stomatitis in some cases (see Pallister, 1949). Either vitamin-B complex or multivitamin tablets were given as long as antibiotics were being administered. Cases were given, when they could take them, at least 2 pints (1.1 l.) of milk, with two eggs as egg-flip, and the juice of two oranges daily until convalescence was clearly beginning.

The results of treatment are analysed in Tables II and III. Cases were divided into "confluent," with more spots confluent than not; "severe," with fewer

spots confluent than not; "moderate," with all spots discrete but hard to count; and "mild," with discrete spots easy to count. The counting area was the face.

The epidemic was characteristically of confluent type and the overall estimated case fatality was 58%. This is compatible with the opinions of various authorities (Ionescu-Mihaesti and Guica, 1945; Frazer and Stallybrass, 1948; Tidy, 1949). The Jiddah series of treated cases in unvaccinated and vaccinated non-Filipinos had case-fatality rates of 44% and 25% respectively, with an overall rate of 39%, showing the modifying effect of vaccination and suggesting the beneficial effect of antibiotic treatment. The treated cases in the vaccinated and revaccinated Filipinos had case-fatality rates of 20% and 11% respectively, with an overall rate of 12%, showing the modifying effect of revaccination and vaccination and again suggesting the beneficial effect of antibiotic treatment.

Clinically, it was noted that patients treated with antibiotics seemed to get over the secondary fever stage without much difficulty, and that the relative absence of pus made nursing less offensive and therefore enabled it to be more effectively carried out. Many vesicles appeared to abort, particularly those on the legs, which, no doubt appearing later in any case, met a stronger level of antibody and antibiotic concentration in the blood. Unpleasant sequelae were rare (see Tables II and III), and it seems probable that these antibiotics shortened the convalescence period.

Five early severe cases in young unvaccinated Arabians were given "aureomycin" orally in daily dosage of 1.5 to 2 g. divided four- or six-hourly, for two or three days (not enough was available for more extensive trial). In three cases it seemed that mental confusion—surprisingly rare in the mass of cases—was directly attributable to the drug, as the symptom disappeared promptly when it was stopped. One patient died. The other four were treated, after the aureomycin was finished, with the dosage of penicillin and streptomycin given to the mass of cases, and they seemed to pass into convalescence with unusual ease; the papules may have been smaller than usual and may have umbilicated more early and dried away more quickly. The drug seems worthy of further trial in the early stages.

Other Clinical Observations

Repeatedly, when moving through crowds of patients, and later when handling quantities of luggage tickets which had been used for bedside clinical records, it was noticed that on moistening the lips a bitter taste was experienced. Movement of the bedclothes or of the labels seemed to accentuate it. It was not noted in contact with chicken-pox, had not been noted before in other circumstances, and has not been noted since. As it was experienced with tickets that had been baked to sterilize them, it cannot necessarily be due to living smallpox virus, but it may have been due to the dead virus or small particles of pock debris. It is of possible interest in view of the belief that smallpox infection may be air-borne.

Most staff on the islands, and most of those repeatedly visiting them, had attacks (one each only) of fever for one or two days or so, and it seems that this was probably "contact fever"—that is, aborted smallpox—there being no initial or focal eruptions. That this "contact fever" was prominent among the discomforts of the Filipinos quarantined on Abu Saad island is shown by Fig. 2, which reveals peculiar oscillations in the records of "fever" in the out-patient clinic, run fitfully when staff was available to give simple treatments for crudely classified minor ailments not requiring the attention of the only doctor available. Among these people no blood films were positive for malaria, splenomegaly was not noted, shivers or sweats were not complained of, and influenza and nasal colds seemed to be absent. Exceptional peaks of requests for "aspirin for fever" were experienced, associated with large numbers of fresh cases of smallpox and exceeding these in value by 100% or more. On the days that the smallpox cases appeared in large numbers the aspirin demands dropped very considerably, suggesting that the fever inspiring them had represented both aborting smallpox and developing smallpox.

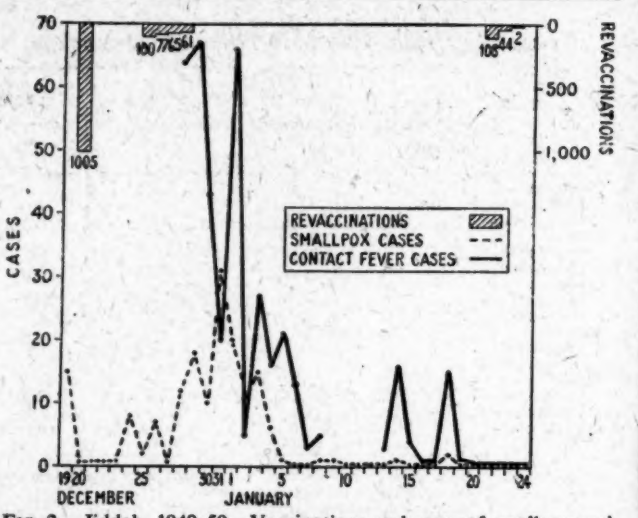


FIG. 2.—Jiddah, 1949–50. Vaccinations and cases of smallpox and contact fever among Filipino pilgrims on Abu Saad island.

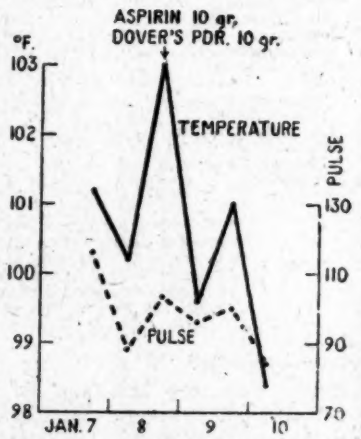


FIG. 3.—Jiddah, 1949–50. Clinical chart of a case of presumed contact fever. The patient was revaccinated on November 20, 1949, and gave an accelerated reaction of immunity. Exposure to infection was constant daily from December 20.

Fig. 3 is the clinical chart of one such case of presumed contact fever. No aches or pains were experienced, merely a little malaise at the height of the fever that disappeared promptly with the sweating after 10 gr. (0.65 g.) each of aspirin and Dover's powder.

Summary

Epidemic smallpox occurred in the Hedjaz in 1949–50, and vaccination and revaccination were effective when properly carried out. One subepidemic in a closed community terminated 14 days after a mass revaccination.

There were estimated to have been 1,000 cases in Jiddah, with an overall case fatality of about 58%.

In revaccinated and vaccinated Filipino pilgrims, those treated with penicillin and streptomycin had a case fatality of 12%.

In vaccinated and unvaccinated non-Filipinos (mostly unvaccinated Saudi Arabians) those treated with these antibiotics had a case fatality of 39%.

Previous vaccination is clearly shown as still the best guarantor of good prognosis in smallpox.

It is considered that penicillin and streptomycin, as administered in these cases, favourably influenced the course of the disease by reducing case fatality, the incidence of serious sequelae, and the duration of convalescence. A particular virtue appeared to be the comparative absence of pus, which made nursing easier.

A few observations on the response of confluent smallpox to aureomycin in young patients with no vaccination experience suggest that the drug is worthy of further trial in early cases.

Two phenomena appearing in association with mass smallpox are illustrated and commented on. They are a bitter taste on moistening the lips, and "contact fever."

The question seems to arise whether all strains of vaccinia used in the preparation of lymph are equally successful in protecting against all strains of variola.

REFERENCES

Frazer, W. M., and Stallybrass, C. O. (1948). *Textbook of Public Health*, 12th ed., p. 315. Livingstone, Edinburgh.

Ionescu-Mihaesti, G., and Guica, M. (1945). *Handbook of Infectious Diseases*, 2nd ed., p. 97. League of Nations, Geneva.

Johnstone, D. F., and Fluker, J. L. (1949). *Mon. Bull. Minist. Hlth.*, **8**, 188.

Pallister, R. A. (1949). *British Medical Journal*, **2**, 1271.

Tidy, H. L. (1949). *A Synopsis of Medicine*, 9th ed., p. 261. Wright, Bristol.

THE NEW GENEVA CONVENTIONS

The International Committee of the Red Cross (7, Avenue de la Paix, Geneva) has issued in volume form the text of the Geneva Conventions which were concluded at the diplomatic conference held at Geneva in 1949. Fifty-nine Governments sent plenipotentiaries to that conference and four others sent observers. Four conventions were established: the first for the protection of wounded and sick in the armed forces in the field; the second for the protection of the wounded, sick, and shipwrecked in the armed forces at sea; the third for the protection of prisoners of war; and the fourth—a totally new convention necessitated by the development of modern warfare—for the protection of civilian persons in an area of hostilities.

A certain background of history is necessary for the understanding of these conventions. In 1863 five citizens of Geneva, the forerunners of the present International Committee, brought the Red Cross into being. The Convention which they established for the amelioration of the wounded and sick in war gave the necessary impetus to the Red Cross movement throughout the world, but, as was only to be expected, it proved to be imperfect, and various proposals for revision were made. In 1906 a diplomatic conference established a revised text, considerably expanding the original, although the fundamental principles of that early treaty remained unshaken. Another diplomatic conference was held in 1929, when the text was again revised in the light of the experience of the first world war. A further diplomatic conference was contemplated for 1940, but was not held. After the second world war the International Committee prepared new drafts. These were examined by experts and by an International Red Cross Conference in 1948, after which they were sent to the diplomatic conference, which opened in Geneva on April 21, 1949. After four months' continuous debate, chiefly in four committees, the final act was signed on August 12. The act was signed on behalf of some 60 Governments, but it does not come into force for the contracting party until six months after it has been ratified by the Government concerned, and many Governments have been very tardy over the formalities of ratification.

Wounded and Sick in the Armed Forces

The first three conventions extend and bring up to date what was already established on behalf of the wounded and sick in the armed forces on land and sea and also for prisoners of war. One provision in the first convention concerns medical staff who fall into enemy hands. Instead of being immediately repatriated, they may in certain circumstances be retained to care for prisoners of war so far as the numbers of such prisoners and their state of health require it. In such cases medical staff—the same applies to chaplains—are not to be deemed prisoners of war themselves, although they are to benefit by all the provisions of the Geneva Convention relating to prisoners. They are to continue to carry out their duties on behalf of the prisoners, preferably those of the armed force to which they themselves belong. In each camp a senior medical officer of the highest rank is to be responsible to the military authorities of the camp for the professional activity of the retained medical staff. It is also provided that medical equipment need no longer be handed back to the belligerent to whom it belongs, but may be reserved for the care of the wounded and sick.

The second convention simply adapts to sea warfare the provisions of the first, and the third convention is framed according to the principle that a combatant who has been captured can be prevented from taking up arms again, but the rights against his person are limited to that, and he must be treated humanely and honourably and released at the conclusion of hostilities. One article (30) reads:

"Every camp shall have an adequate infirmary where prisoners of war may have the attention they require, as well as appropriate diet. Isolation wards shall, if necessary, be set aside for cases of contagious or mental disease."

Prisoners who need special treatment, a surgical operation, or hospital care are to be admitted to any civil or military medical unit where such treatment can be given, even if their repatriation is contemplated in the near future.

Protection of Civilians in Wartime

The fourth convention, entitled "Geneva Convention relative to the protection of civilian persons in time of war," has been long awaited. The idea of it was first mooted at the end of the first world war, when it became clear that civilians were exposed to the same—sometimes even greater—dangers as the armed forces. A new idea in this convention is the setting up of hospital and safety zones and localities. Article 14 reads:

"In time of peace the High Contracting Parties and, after the outbreak of hostilities, the Parties thereto, may establish in their own territory and, if the need arises, in occupied areas, hospital and safety zones and localities so organized as to protect from the effects of war, wounded, sick, and aged persons, children under 15, expectant mothers, and mothers of children under 7. Upon the outbreak and during the course of hostilities, the Parties concerned may conclude agreements on mutual recognition of the zones and localities they have created. . . ."

For this purpose a large medical staff will be needed, and staff on such duty will have the benefit of all the protection the zone offers as a return for their services. A slightly different conception appears in a later article (15) concerning neutralized zones:

"Any Party to the conflict may, either direct or through a neutral State or some humanitarian organization, propose to the adverse Party to establish in the regions where fighting is taking place, neutralized zones intended to shelter from the effect of war the following persons, without distinction: (*a*) wounded and sick combatants and non-combatants; (*b*) civilian persons who take no part in hostilities, and who, while they reside in the zones, perform no work of a military character."

These zones are more temporary in character, and, apart from the wounded and sick, would afford refuge to all not directly taking part in the fighting. Perhaps the article of greatest interest is that dealing with the protection of hospitals. Civilian hospitals may in no circumstances be the object of attack, and are to be marked with the distinctive

emblem clearly visible to land, air, and naval forces. They should be situated as far as possible from military objectives. The protection to which they are entitled will, however, be discontinued should they be used to commit, outside their humanitarian duties, acts harmful to the enemy.

Another article (23) enjoins the free passage of all consignments of medical and hospital stores and of essential foodstuffs, clothing, and tonics intended for children under 15, expectant mothers, and maternity cases.

Finally, a word may be said about the employment of the Red Cross emblem. The armlet may be used by doctors if they belong to the staff of a Red Cross or other voluntary organized relief society attached to the military medical service, subject to military laws and regulations, and employed on the same duties, and civilian doctors may display the emblem if they are on the regular staff of a recognized civilian hospital, but only in occupied territory and in a combat zone. Medical orderlies or stretcher bearers are entitled to an armlet, on which the Red Cross will be of reduced dimensions, but only to be used while searching for, collecting, transporting, or treating the sick and wounded. All other employment of the emblem is forbidden.

The four conventions contain altogether 429 articles, with 11 annexes. To quote from a draft preamble, submitted by the French and Finnish delegations—but not adopted, because it was resolved to follow the precedent of other Geneva conventions and have no preamble—they are "inspired by the eternal principles of that law which is the foundation and safeguard of civilization" and designed "to ensure respect of human personality and dignity by putting beyond reach of attack those rights and liberties which are the essence of its existence."

CONGRESS OF ANAESTHETISTS

SCIENTIFIC SESSIONS

In the first three days of the Congress of Anaesthetists, 23 papers were read and discussed at the Scientific Sessions held in the Old Library of B.M.A. House; those of interest beyond the specialty itself are included in this report.

Dr. C. METZ, President-elect of the American Society of Anesthesiologists, took the chair on the first day, when Dr. P. A. LIEF, of New York, and Dr. B. B. BRODIE, of Bethesda, Maryland, destroyed in two short papers the established conception of the behaviour of the "ultra-short-acting" barbiturates in the body. Dr. Brodie recalled that anaesthetists knew well enough that a small dose of thiopentone produced brief anaesthesia, and that after repeated injections it was no longer a short-acting drug but caused prolonged narcosis. He had estimated the concentration of thiopentone in different tissues by a specific method depending on the absorption of ultra-violet light. His work showed that the concentration of thiopentone in the plasma fell rapidly after the administration of a single small dose, but after 30 minutes the rate of decline was much reduced, and after 1–2 hours it fell to 10–15% per hour. This figure represented the true rate of destruction of thiopentone; the early sharp decline in the plasma concentration was due to distribution of the drug in the body. Studies carried out in dogs two and a half hours after a single large dose showed that the concentration of thiopentone in fat was 6–12 times that in plasma, and that the fat depots contained 70% of the dose. In man the rapid localization of a small dose of the drug in fat left the plasma level below that necessary for narcosis, and the subject woke up; after a large dose or repeated doses the plasma level of thiopentone was maintained above the anaesthetic level by the reservoir of the drug in fat. As thiopentone was, in fact, slowly metabolized, the narcosis then continued for some time. Dr. Brodie explained that patients acquired an acute tolerance to thiopentone, and after large doses might awaken when the plasma levels were much above those which would maintain deep anaesthesia immediately after small doses. He found that thiopentone was distributed evenly through the brain. Pentobarbitone, which differed in structure from thiopentone only in having an oxygen atom in place of a sulphur atom, was well known as a longer-lasting anaesthetic; this drug was not localized in fat in the same manner as thiopentone, and the length of its action therefore depended only on the rate at which it was metabolized.

Dr. LIEF described his study of this class of barbiturate in man. He found that there was an appreciable concentration of thiopentone in the plasma as long as 40 hours after injection, and he emphasized the cumulative effect of these drugs when the fat depots of the body were saturated. The barbiturates were hypnotics, not anaesthetics, for they had no analgesic or relaxant effect; they should be used only as supplementaries to general anaesthesia. There was a need in anaesthetic practice for an unstable compound that would have a truly ultra-short action in the body.

New Curarizing Agents

On the third day of the congress Dr. G. F. V. ANSON, of Auckland, New Zealand, took the chair in place of Dr. WESLEY BOURNE, who was unable to attend. Two new curarizing agents were described by workers from Italy and Sweden. Dr. R. OTTOLENGHI, of Rome, introduced a new short-acting drug, "3621.S," or "tachycurine." This was a synthetic agent, as powerful a relaxant as D-tubocurarine but with a maximum duration of 2–3 minutes. Given intravenously it produced an effect in man in one-fifteenth of the time taken by D-tubocurarine. The rapidity of its effect was due to the speed with which the drug was hydrolysed in the body. Dr. Ottolenghi and his colleagues had used the drug in 80 cases since 1949. It was given in a 2% solution (which is miscible with thiopentone) in doses of 60–400 mg. Supplementary doses of 10 mg. could be given every five minutes. The drug had no effect on the heart, liver, or kidneys, but muscular tremors occurred, particularly after rapid injection, and salivation was considerable even when large doses of atropine had been given. There was no antidote to the drug, and eserine prolonged its action. Dr. C. F. SCURR, of the Westminster Hospital, described his satisfactory use of the drug in 40 patients.

Dr. S. THESLEFF, of Stockholm, gave an account of the experimental investigation of succinyl-choline-iodide, a short-acting relaxant developed at the Karolinska Institute, Stockholm. It had no effect on blood pressure in animals or man, apart from producing a slight rise; it did not cause the production of histamine, and therefore had no danger of initiating bronchospasm. As the drug broke down quickly in an alkaline medium it was not suitable for mixture with thiopentone. Neostigmine caused prolongation of its action. Dr. O. VON DARDEL, also of Stockholm, gave an account of clinical trials of the drug, which he had used in 1,000 cases—132 of these for major operations and 512 for electric convulsion therapy. It had been given in thoracic surgery and neurosurgery, administered to patients of all ages above infancy, and used with all the customary general anaesthetics as well as to reinforce spinal analgesia. He had employed it for intubation in doses of 60–80 mg. Muscular twitching occurred 60 seconds after injection, but this rapidly ceased and complete relaxation was obtained. He found that prolonged action was best achieved with an intravenous transfusion of the strength of 1 mg. per ml. of saline, administered at a rate of 40–60 drops (2–3 mg.) a minute. The average patient required 200 mg. an hour, and if there was danger of too much fluid being given a stronger concentration could be used. There had been no

complications. Dr. MYERHOFFER, of Vienna, described experiments he had made on himself with the drug. He had found it a satisfactory agent, but he preferred the chloride, since it was a more stable compound and was miscible with thiopentone.

Obstetrical Analgesia

The afternoon session, which was held under the chairmanship of Dr. G. COUSINEAU, of Montreal, was concerned mainly with anaesthesia and analgesia in obstetrical practice. Dr. J. G. P. CLELAND, of Oregon, described the technique he used for continuous epidural and caudal block in obstetrics and for post-operative analgesia. He obtained continuous relief of pain after operation by injecting into the epidural space every 1½–2 hours 4 to 8 ml. of buffered 0.25% amethocaine hydrochloride or 0.4% of "nupercaine," with adrenaline. The syringe was clipped to the head of the patient's bed, and Dr. Cleland explained that it was just as simple to provide this form of analgesia as to administer a hypodermic injection every four hours. The inhibition of respiration that normally followed abdominal operations was relieved if the nerve supply to the wound was interrupted in the epidural space: meteorism was less and headache did not occur; less narcotics were given; the healing of the wound was quicker; and the patients became ambulatory much earlier.

Dr. J. H. CANTAROW, of Beverley Hills, California, began his paper on continuous caudal analgesia in private obstetrical practice with two contradictory pleas: that more caudal analgesics should be given, and that none should be administered at all if they could not be performed correctly. He emphasized that women in the United States were so familiar with accounts of new obstetrical analgesics in the newspapers and magazines that they believed suffering was no longer necessary in childbirth. He described the spread of Hingson's caudal technique, which was poorly received in 1942 because of the distraction of the war, given a bad name later because it was mishandled, and then grew in popularity when it was practised correctly. The usual objections to Hingson's method could be abolished by careful technique; the deaths that had occurred under it resulted from inadvertent intravenous or spinal injection of the analgesic drug. It was a good method with premature babies because absorption of the drug was slow, and it did not therefore affect the child. Dr. Cantarow admitted that occipito-posterior positions were more frequent with this technique, but the child could be more easily rotated; forceps were required more often, but the "prophylactic" forceps administration was normal practice in the United States. His personal experience was that caudal block gave better results than any other form of analgesia, and he described the use of an instructional film, of music, and of the other adjuncts to delivery usual at the Cedars of Lebanon Hospital, which transformed childbirth into "a cheerful experience."

Italian and British Viewpoints

Professor A. M. DOGLIOTTI, of Turin, spoke of his 26 years' experience of epidural analgesia, which he believed to be the best form of conduction analgesia. He used a continuous caudal analgesic after perineal operations, leaving a flexible needle in place for 24 to 48 hours. He described a new method for the relief of intractable pain: a catheter was introduced into the epidural space and 2% procaine or xylocaine was injected every two to three hours in doses of 10 to 12 ml. for five to six days. The patient was ambulant during this period. This produced relief of pain, but did not affect the motor fibres or those carrying other sensation. His first patients began treatment four months ago, and have since been continuously free from pain.

Dr. A. E. PALETTO, of Turin, reviewed 1,639 administrations of epidural analgesia for thoracoplasty in 800 patients. He described his results as "most satisfactory," and explained that no death had occurred which was attributable to the analgesic.

Dr. E. H. SEWARD, of High Wycombe, represented the British viewpoint on obstetrical analgesia. He believed that adequate analgesia could be obtained in 90 to 95% of normal confinements by a combination of psychological management and relaxation in the antenatal period, and the use during labour of small doses of analgesic drugs with the intermittent inhalation of an anaesthetic. The inhalation should be used towards the end of the first stage of labour, for the second stage, and for delivery. The best agents for this purpose were 75% nitrous oxide with 25% oxygen, and 0.5% trichlorethylene in air. Intermittent inhalation analgesia had the advantages of being self-administered and providing the mother with something active to do which she felt was a direct contribution towards the progress of labour. It could be safely supervised by the midwife conducting the labour, and the anaesthetic gases used did not prejudice the initiation of respiration in the baby.

An account of the scientific sessions of the last two days of the Congress will appear in next week's *Journal*.

SECOND INTERNATIONAL POLIOMYELITIS CONFERENCE, COPENHAGEN

TREATMENT OF POLIOMYELITIS

The discussion held on September 6 was not concerned much with the acute stage of the disease, owing perhaps to the uncertainty caused by the many advances reported by virologists, which seem likely to lead to revolutionary changes in treatment before long.

JAMES L. WILSON (Michigan) reviewed the management of respiratory insufficiency. He distinguished between respiratory failure due to paralysis of respiratory muscles, failure due to pharyngeal paralysis with secretions which mechanically obstruct the larynx, and failure due to central involvement of the respiratory centre. In considering the use of respirators for the first group he referred to the biochemical problems involved and the need to avoid over-ventilation. He described various devices for maintaining respiration by intermittent positive pressure applied to the face when the respirator is not operating. In cases of pharyngeal paralysis postural drainage, especially in the prone position, is life-saving in many such cases; suction devices to remove secretions are also necessary, but must be used with care and skill. In some cases tracheotomy is necessary, but the correct indications for this are still uncertain.

Paralysis of the Upper Limb

H. J. SEDDON (England) reported his experience of operations on the upper limb (proximal to the hand) designed to improve its usefulness when partially paralysed. He said that no such operations should be carried out unless some use could be made of the hand. The full mobility of all joints must of course have been maintained. Arthrodesis should not be lightly undertaken, and certainly not under 14 years of age. Necessary tendon and muscle operations should not, however, be long delayed. So far as the wrist is concerned, any necessary tendon transplants should be carried out before the need for arthrodesis is decided.

At the elbow arthrodesis for paralysis of flexion is avoided if possible, and transplantation of the lower part of the pectoralis major or the proximal transplantation of the common flexor origin are often useful. Operations on the shoulder should be undertaken only after much deliberation, and generally as a last step. If arthrodesis is decided on Mr. Seddon pegs the humerus to the glenoid with a fibular graft—the functional result is generally more comfortable and useful if the angle of fixed abduction is only 15°–30°.

CHARLES E. IRWIN (Warm Springs, Georgia) described a variety of operations designed to restore the power to pinch between the thumb and fingers where partial paralysis was disabling. He laid special emphasis on a transfer operation in which the tendon of flexor digitorum sublimis to the ring

finger is passed round the lower end of the tendon of flexor carpi ulnaris and then laterally to be inserted into bone at the ulnar border of the base of the proximal phalanx of the thumb. Many modifications of this operation were described and also a variety of other surgical procedures to improve the usefulness of partially paralysed hands.

Scoliosis

JOHN R. COBB (New York) described his experiences of treating 165 patients with post-polio-scoliosis. He strongly criticized those who maintain that this or that method of treatment avoids scoliosis: either such therapists do not look at the spine or they do not follow the case for long enough. Polio cases must be watched for several years when there has been trunk paresis. Asymmetry of muscle power almost inevitably leads to scoliosis sooner or later. The degree of deformity in the adult never reaches the extremes seen in children.

In the treatment of established deformities the hinged turnbuckle jacket is valuable. In many cases spinal fusion is highly satisfactory and enables the patient to dispense with cumbersome appliances. The optimum age for spinal fusion is 14–16 years—a massive and mature fusion is required. The operation should never be done at an early age. The use of crutches and a tripod gait may be required in young patients to avoid the harmful effects of walking with asymmetical spinal muscles. Soft-tissue operations are not effective.

Physical Medicine

ROBERT L. BENNETT (Warm Springs, Georgia) spoke on physical medicine in poliomyelitis. He said that there had developed a greater realization of the physician's responsibility in all three stages of the disease. These he described as the phase of medical emergency, the phase of neuro-muscular recovery, and the phase of adaptation to residual physical handicaps. In the first stage gentle measures must be used and over-enthusiastic interference might be dangerous. The early tendencies for muscle tightness to develop in certain muscle groups must be recognized and countered. Dr. Bennett emphasized the need to train the patient to use the functioning muscles in the most effective way, and favoured tedious and meticulous coaching in muscle education as a prelude to functional training. He considered that over-use of weak muscles during the first six to nine months after the onset of poliomyelitis is harmful, though the reason for this is not known. Activity is a necessary part of convalescence, but this must be safe, and supportive apparatus is an essential part of convalescence.

Social Problems

ALICE BRUUN (Copenhagen) spoke of the social problems of poliomyelitis. In Denmark all severe cases are admitted to hospital. Long-term financial assistance for the severely disabled should be a responsibility of the public authority. For children special schools and workshops are required, but training should be for work which is of interest to the patient and in which there is a reasonable prospect of obtaining employment. For the severely disabled adult many serious problems arise and expert advice is required on the best line of action. Special instructions should be available for the most severely disabled. Severely disabled victims will benefit from the system of allotting a "counsellor" to investigate all his personal problems and to plan with social workers and doctors how to make the best plan for the future.

MORTON A. SEIDENFIELD (New York) spoke of the psychological aspects of poliomyelitis. Various studies have shown that the disease is not followed by any loss of intellectual capacity. Parents tend to over-indulge the patient, and then when finding him "spoiled" revert to excessive severity, which causes remorse. Various factors involved in emotional disturbances have been described, such as parental rejection, over-aggressiveness, withdrawal reaction, and various environmental and parental influences.

DISINFECTANTS AND DISINFECTION

At the British Pharmaceutical Conference held at Harrogate this week the chairman, Professor H. Berry, gave on September 11 a "Review of Disinfectants and Disinfection." He discussed first the question of the evaluation and standardization of disinfectants, and strongly criticized the Rideal-Walker test and so-called phenol coefficient, which was often intentionally misused in advertisements to gull the uninformed layman. In biological assay it was essential always to compare like with like, and this the Rideal-Walker test did not do, since it matched every new disinfectant (no matter what its chemical nature) against a standard phenol solution, comparing the concentrations of the two substances which would kill *Salmonella typhi* in distilled water at 18°–20° C. in a specified time. Changing any of the conditions, the killing time, the temperature, or the test organism changed the results and gave a different estimate of disinfectant power. Many hospitals were inclined to use the chloroxylenols instead of the old-fashioned lysol, and, though these newer disinfectants were very powerful against the typhoid bacillus, they were usually very poor against pathogenic staphylococci.

Professor Berry wished that hospitals would seek expert advice before changing to these new preparations. Unfortunately there was no official body to adjudicate on new disinfectants as the Medical Research Council sometimes did on new drugs, and as the U.S. Department of Agriculture (through the Food, Drug, and Cosmetic Act) and the American Medical Association (through its Council on Pharmacy and Chemistry) do in the United States. It was true that the Milk and Dairies Regulations, 1949, specified strengths of hypochlorite for use in dairies, and this beginning should be followed up by the Ministry of Health.

Judging New Disinfectants

Professor Berry listed seven preliminary sorting tests:

1. Effect of variation of time, temperature, and dilution on bactericidal power.
2. Effect of these variations with a variety of organisms, including spores, and in the presence or absence of blood and other organic matter.
3. Bacteriostatic values.
4. Skin irritation and tissue toxicity tests.
5. Oral toxicity tests.
6. Tests of effectiveness with animals.
7. Effect of possible inactivators.

He considered that this detailed evaluation was the only way to define a disinfectant's suitability. Standards of chemical purity could be set up for most disinfectants, and for the remainder individual biological tests against a whole set of standards was the answer. Development would be in the direction of special disinfectants for special jobs rather than trying to find one good all-round preparation. Thus the quaternary ammonium compounds, one of the most interesting and promising disinfectant groups of recent years, had special value for washing wounds, because, as well as being bactericidal and detergent, they were non-irritating and relatively non-toxic.

Inactivators or Revivers

In 1881 Koch claimed that mercuric chloride was a powerful and reliable bactericide, but in 1889 Geppert showed that it was merely inhibitory. Bacteria appeared dead because they would not grow in culture solution, but they would still multiply if after several years they were removed and washed with ammonium sulphide. Disinfectants such as mercuric potassium iodide, "merthiolate," "metaphen," and mercurochrome were all purely bacteriostatic in this way, and evidence was accumulating that the glutathione present in tissues would reverse their action, and might allow pathogenic organisms to multiply. Phenol was a true bactericide, but revivers had been found for iodine, the hypochlorites, and formaldehyde.

Nova et Vetera

RESUSCITATION IN 1741

BY

S. WOOD

Library Assistant, Royal College of Surgeons of England

A little-known account of a case of recovery from prolonged drowning is to be found hidden away in a pamphlet on smallpox inoculation published in 1768.[1] Jane Brown, aged 23, seized with the smallpox, threw herself, while delirious, into the New River at Islington at midday on November 21, 1741. She was first seen, floating face down, by an old man on the opposite side of the river who went round as fast as he could to give the alarm at the Crown alehouse, which was situated at some distance from the river. No one knew how long the woman had been in the water, and when brought ashore she showed not the least appearance of life.

After much altercation about which parish should bury her—Clerkenwell or Islington—the parish grave-digger, William Stevens, and Thomas Bull, a parish-bearer, were sent to bring the body to the workhouse at St. James's, Clerkenwell. While carrying her in a coffin across the fields Bull's foot slipped on the frosty grass and the body fell to the ground. As the men lifted her to their shoulders they fancied they heard a faint sort of groan. They reported this circumstance at the workhouse, where she was laid upon the lid of the parish coffin under an open arch going into the infirmary, the usual repository for the dead before interment.

While some people were looking at her they noticed a little motion in the upper lip, whereupon the master of the workhouse ordered her to be put to bed and Mr. Oborne, "a very reputable surgeon and apothecary at Clerkenwell," to be summoned. When the surgeon arrived about three hours had passed since she had thrown herself into the water. On examination Mr. Oborne found the woman extremely cold, stomach much swollen, without pulse, and to all appearance dead. However, the surgeon attempted recovery by pouring down her throat a spoonful of warm water well impregnated with spirit of hartshorn, meanwhile having her smartly rubbed with coarse cloths and rolled backwards and forwards upon her stomach and sides. While this was being done an odd croaking noise was heard and this was followed by a sudden gust of wind and water. She was instantly turned face down with her head inclining over the edge of the bed to help the discharge of water, which now ran freely from her mouth to the floor.

When this flow had ceased she was turned on her back with her head a little raised. The distension of the stomach had quite abated. As Mr. Oborne had no other medicine than the spirit of hartshorn, he boiled a little ginger sliced in some water, and after straining it added an equal part of mountain wine. The woman still appeared to be dead, but at this point a trembling motion was perceived in the lower jaw. The surgeon then administered three or four spoonfuls of the warm ginger mixture and laid a hot flannel petticoat over her stomach and bowels. This shortly caused a surprising kind of rumbling which was succeeded by a powerful discharge of wind from her stomach, and then a little motion was seen in one arm. More ginger and wine was given, and for the first time it was possible to discover a slow, creeping pulse. Her stomach was a little warm, but her extremities were still cold. These were wrapped in warm flannel, and as more medicines had now arrived she was given three spoonfuls of Ralegh's confection, salt of hartshorn, and tincture of cardamom.

About 8 o'clock in the evening the patient could turn herself in bed, was much warmer, and had taken a little broth and bread. Early next morning it was found that the smallpox had broken out all over her. Her pulse was now "finely raised." She had made much urine in the night, complained of being sore all over, and was so hoarse she could scarce be understood. The medicine was continued, together with a pectoral drink which cured the hoarseness by next day, when the patient was able to sit up in bed.

On the fourth day the smallpox pustules began to suppurate kindly, and by the end of the week these were all turned. The patient was now eating heartily, had a temperate degree of heat, and two or three days later was walking about the ward with no other complaint than that of extreme hunger.

The author of the pamphlet ends his account by urging the attempted recovery of those recently drowned, however lifeless they may appear to be. In this desperate case treatment had been successful, though the woman's last chance of survival would seem to have been removed by placing her body on the lid of a coffin under an open arch exposed to the cold November air.

Whether the smallpox fever ensured a reserve of vital heat sufficient to ward off dissolution is a matter for physiologists to consider.

[1] William Watson, M.D., F.R.S.: "An Account of a Series of Experiments, Instituted with a View of Ascertaining the Most Successful Method of Inoculating the Small-pox." London, 1768.

SIR WILLIAM WHITLA (1851-1933)

Sir William Whitla, the centenary of whose birth occurs to-day (September 15), served an apprenticeship with a firm of dispensing chemists in Belfast before studying medicine, and the intimate and practical knowledge of drugs acquired during this period was to prove most useful in his distinguished clinical career. In 1877 he graduated M.D. at Queen's College with first-class honours and a gold medal. Before he was 30 he was appointed physician to the Royal Victoria Hospital, and he rapidly acquired a large private practice, his success being due not only to his professional skill but also to a remarkable character which inspired patients to give him their confidence and affection.

Whitla's appointment in 1890 as professor of materia medica and therapeutics at Queen's College was welcomed by the students, for his lectures were always coloured by his sense of the dramatic. A devoted student of English literature, who made the Bible and Shakespeare his constant companions, his conversation, generously sprinkled with apt allusions and quotations, was a sheer delight.

Two books made Whitla's name familiar to generations of medical men—the *Elements of Pharmacy, Materia Medica, and Therapeutics*, first published in 1882, and the *Dictionary of Treatment*, 1891. The first edition of the *Dictionary*, in which every article was from Whitla's own pen, was so popular that its 8,000 copies were sold within nine months and 2,000 copies of the American edition had to be imported to help meet the insistent demand.

In 1910 Whitla represented Queen's University on the General Medical Council, and, elected its first Member of Parliament in 1918, for his five years of office was a watchful champion in the interests of education. When the British Medical Association met at Belfast in 1909 Whitla, as the foremost medical figure in the city, was elected President, and his energy, urbanity, and hospitality made it one of the most successful meetings in the Association's history.

Whitla's benefactions were numerous and often secret. One generous gift, however, stands to-day as a memorial to one who always had the interests of the profession at heart. The Medical Institute, Belfast, designed to house the Ulster Medical Society and now known as the Whitla Institute, was built and equipped at his expense. Recipient of many honorary degrees, Whitla was knighted in 1902 and appointed honorary physician to the King in Ireland. He died on December 11, 1933.

Correspondence

Laryngeal Epilepsy

SIR,—In their interesting article on "The 'Mess Trick' and the 'Fainting Lark'" (August 18, p. 382) Professor E. P. Sharpey-Schafer and his colleagues have, I think, shed further light indirectly on that elusive will-o'-the-wisp of medical literature—"laryngeal epilepsy."

Noted briefly by Sydenham (1679) and more fully described by Charcot (1876) under the name "laryngeal vertigo," the condition has been observed chiefly in men between early and late middle age who are quite commonly of stocky build and emphysematous or "chesty"; they often smoke and drink fairly liberally. The victim has an attack of coughing which is usually, though not always, severe, feels dizzy or faint, then abruptly loses consciousness and falls to the ground, when convulsions may occur. Duration is measured in seconds; recovery is almost instantaneous, apart, it may be, from slight headache and tiredness. Consciousness is not always lost; mental confusion, blacking-out, or "swimming" of the visual fields or clouding of consciousness may be the only experience.

Since Charcot's time and until quite recently the cause has been regarded as epileptic, French clinicians, in fact, differentiating major and minor attacks: so-called *ictus laryngé* (fearsome hybrid!) when consciousness was lost and convulsive movements occurred, and *vertige laryngé* when dizziness only resulted.

Three main theories of causation have been proposed: (1) Reflex (from the larynx), (2) epileptic, (3) cardiovascular.

The best appraisal of these, and a general description of the condition up to the present, is, I believe, by Baker (1949).

The reflex cause is untenable; the epileptic unlikely, either as a cough aura in grand mal or a reflex epilepsy; the cardiovascular remains.

The influence of cough on the cardiovascular system differs, on the one hand if it occurs with alternate inspiratory and expiratory efforts, or on the other with predominantly expiratory efforts against a closed glottis. Only the latter produces marked effects. The blood flow through the lungs is diminished as the intrapulmonary pressure is raised; the intrapleural pressure rises rapidly, probably up to +15 or even +50 mm. Hg; venous return is therefore impaired, and together with the resulting venous congestion of the head and neck the stroke volume of the right (and therefore left) ventricle falls, after a brief and initial rise has occurred. This chain of events leading to deficient cerebral blood supply is thought to cause unconsciousness. This, in a nutshell, is Baker's view, though he himself has not performed experiments to adduce it.

Rook (1946), noting R.A.F. recruits performing Flack's test, in which a column of mercury is blown to a height of 40 mm. and maintained as long as possible, observed occasional cases of unconsciousness, and thought cerebral congestion to be largely the responsible agent. However, cerebral congestion produced by negative acceleration either in an aircraft or in giant centrifuges (Armstrong, 1939) seldom appears to produce unconsciousness.

Both coughing against a closed glottis and Flack's test are close analogues of Valsalva's manœuvre. Previously, Wilkins and Friedland (1944) observed loss of consciousness in some normal subjects performing this manœuvre, diminution of venous return and cardiac output being recorded by the ballistocardiograph.

It appears to me probable that venous congestion of the head and diminution in cardiac output produced by coughing against a closed glottis are likely to produce a fall in the pressure gradient across the intracranial arteriovenous circulation similar in effect to and corresponding to that produced by the over-breathing and Valsalva manœuvre of the "Mess Trick," though the exact intracranial mechanics are no doubt slightly different. McCann *et al.* (1949), using the cardiac catheter, compared the pressures in the right ventricle during the Valsalva manœuvre and during coughing; in both cases they were raised, but during coughing pressures as high as 300 mm. Hg were recorded. Repeating this experiment with a bronchoscope *in situ*, Valsalva's manœuvre was clearly impossible, but right intraventricular pressure still rose to 250 mm. Hg on coughing. Various vasodilatory drugs were later employed to examine the possibility of pulmonary artery spasm being in part responsible for this rise in pressure, but results were not conclusive. It seems unfortunate, however, that this part of the experiment was not repeated with the bronchoscope in position.

Though I have nothing new to say about the condition, Sir, I am of the opinion that the theoretical cardiovascular aetiology summarized by Baker has been fairly well born out by experiment, and Professor Sharpey-Schafer's recent work in the realm of schoolboy pranks appears to add considerable further support. The possibility of pulmonary artery spasm occurring during these attacks still, so far as I am aware, remains to be shown.

Theoretical considerations to one side, "laryngeal epilepsy," rather than the rarity it has been supposed to be until recent times, is probably fairly common; it is more likely to be seen (or heard of) by the general practitioner than by the consultant or hospital doctor. Knowledge of the condition in major or minor form, and its causation, are important in differential diagnosis, yet it hardly appears in modern textbooks of medicine. While referred to as an "epilepsy" for many years, it appears to be caused by the simultaneous triad of cerebral anoxia, cerebral venous congestion, and sudden reduction in effective cerebral arterial pressure. Either the term "cough syndrome" proposed by Baker or "tussive syncope" proposed by McCann therefore seems preferable. The possibility of an occasional case being due to hypersensitivity of the carotid sinus during coughing is thus not overlooked.—I am, etc.,

London, N.W.10. W. RAYMOND PARKES.

REFERENCES

Armstrong, H. G. (1939). *Principles and Practice of Aviation Medicine.* Baillière, Tindall and Cox, London.
Baker, C. (1949). *Guy's Hosp. Rep.*, **98**, 132.
Charcot, J. M. (1876). *Gaz. méd. France*, **7**, 588.
McCann, W. S., *et al.* (1949). *Arch. intern. Med.*, **84**, 845.
Rook, A. F. (1946). *Brain*, **69**, 138.
Sydenham, T. (1679). See Major, R. H., *Classical Descriptions of Disease*, 1945. p. 201. Springfield, Ill.
Wilkins, R. W., and Friedland, C. K. (1944). *J. clin. Invest.*, **23**, 939.

Penalties for Sexual Offences

SIR,—Surely Dr. H. Ward-Smith (September 1, p. 549), in his haste to indulge in polemic, has missed the point of Dr. G. W. Fleming's letter? When an elderly married man of good character with grown-up children of his own assaults juveniles of either sex, the chances are that change of personality due to organic disease of the brain, probably arteriosclerosis, caused the crime. In the Press reports which I read about the trial medical evidence was not mentioned, so presumably none was given.

No one denies that people of good character can control sexual aberrations, while people of poor character cannot, but cerebral organic disease may prevent even a person of the best character from exercising ordinary control. In a case of this sort imprisonment, degradation, and the loss of a pension gained by years of honourable service to the Crown are in my opinion an exceedingly harsh punishment. The place for an old man unable to control himself is in a hospital, where he can be under care and supervision for an indefinite period: not a prison, from whence in about 12 months he will emerge probably more irresponsible and as much a menace to the young as ever.

It is inappropriate to discuss the wider question of the correct treatment of sexual offenders in this context; but the desire to cling to punishment for punishment's sake is as sentimental as the wish to do without it altogether, and of the two errors the latter is the less fatal to humanity.—I am, etc.,

Godalming. HUMPHRY OSMOND.

SIR,—Dr. H. Ward-Smith (September 1, p. 549) says I am indignant because a man of some standing and education has been sent to prison for 18 months for improper offences and I consider the penalty is out of all proportion

to the crime. "Let him think again," he says. I have, and would ask him to do likewise and explain why he has omitted to mention the part of the penalty—viz., the loss of £1,000 per annum pension—which I consider out of all proportion to the crime. For that, according to the Press report, is part (and far the heaviest part) of the penalty the offender has had to pay, and not only himself but his dependants too. If Dr. Ward-Smith does not think that penalty is out of all proportion to the crime I hope few will agree with him.

My appeal to the medical profession was not to condone but to give a lead towards more humane and enlightened consideration of these offences. For, so long as they are approached in a spirit of obscurantism, self-righteousness, and moral indignation, justice is sure to suffer and vindictive penalties to gain support.—I am, etc.,

Gosport. G. W. FLEMING.

SIR,—Apropos of the recent correspondence on this subject in your columns, it would be interesting to know of any objection to castration as a legal cure for sexual offences on boys and girls. Surely the proper way to treat a man who has been convicted of corrupting children is to remove his testicles. This treatment would be cheaper than imprisonment, would cure the criminal of his evil propensity, and would protect the public. Moreover, the prospect of such an operation would act as a deterrent.—I am, etc.,

Marlborough. HAROLD BURROWS.

SIR,—After 60 years of practice, about half of which was spent in mental hospital work, I am greatly concerned at the serious increase of crime, mostly by sexual perverts against children, and would suggest instead of hanging the murderer a more rational treatment, viz., castration of the culprit, preceded and followed by a course of psychotherapy, thus making him harmless for the future, and also avoiding waste of life. In minor cases of the same offence I would suggest the same treatment. So often these perverts have hidden stores of brilliance, as in Oscar Wilde.

Though 93 years of age, I am still very interested in all that concerns mental health.—I am, etc.,

Steanbridge, near Stroud. W. W. HORTON.

SIR,—I am sure many of your readers will share the opinions of Dr. H. Ward-Smith (September 1, p. 549). I find it difficult to believe that Dr. G. W. Fleming (August 11, p. 363) would write as he did if he were the father of sons. My wife and I have watched the growth to manhood of our five boys, and we always hoped and prayed they and we might be spared the horrors of sodomy. I should very much like to know how Dr. Fleming would proceed to treat this particular case. If "the crime was a disorder of the body and mind," a man in the position of rear-admiral could secure, if he so desired, medical and surgical treatment.

To be honest, is not homosexuality fundamentally a moral disease, and are we not on the stage and in modern literature becoming more than condoning? In the case referred to the punishment may sound severe—but "not out of all proportion to the crime." Can it in any way wipe out the distorted and unnatural view of sexual affairs the five young victims have encountered? Probably some of us for various reasons may be more prone than others to temptation in this direction, but may I submit that the greatest deterrent is a healthy, fearless public opinion and the sort of treatment which has most justly been meted out in this particular case?

Punishment in these cases is not a vindictive act but administered for the good of the community and to act as a deterrent to the culprit himself and the rest of us. I fancy if I were tempted to yield in this direction I should hesitate if I knew I should lose my income, go to gaol, and especially if I might expect a good thrashing for each boy whose outlook on life I had so smirched. However merciful we may pride ourselves that we are in our judgments of others, we cannot forget that God, "who is rich in mercy," destroyed Sodom for the sin which has given its name to this ugly perversion.—I am, etc.,

Winchester. G. ORISSA TAYLOR.

Treatment of Migraine

SIR,—I am surprised to see that in the annotation (September 1, p. 538) no mention is made of the use of ergometrine in this condition. I drew attention to this same matter in my letter in the *Journal* of November 24, 1945 (p. 745), shortly after a similar publication on this subject.

Because ergotoxine and ergotamine are both toxic substances, they are contraindicated as a form of treatment for any condition if a suitable and effective alternative is available. Ergotamine, the less toxic of the two, is used in migraine generally by injection, because of its poor solubility in water and unreliable effect by mouth. Ergometrine is water-soluble, well absorbed, and rapid in action by mouth, as we know from the fact that it will induce uterine contractions post-partum in as short a time as eight minutes after being swallowed, and, perhaps more important still, it is non-toxic in the human subject in therapeutic doses. It is true that not quite as many patients with migraine can be treated satisfactorily by ergometrine by mouth as can be by injections of ergotamine. However, owing to its non-toxicity and the convenience of being able to swallow a small tablet by mouth, 0.5 mg. is usually sufficient, and it should always be tried initially in these cases, and resort to ergotamine injections only be made for those cases that do not respond.

So far as nausea is concerned, which seems common to the central action of these ergot alkaloids, this is also produced by ergometrine. I have never, however, had anyone who benefited by ergometrine but considered giving it up because of the nausea induced. More commonly, although the nausea itself is of course disliked, its onset is welcomed as coincident with the commencement of rapid improvement of the headache. It may be, of course, that the nausea produced by ergometrine orally is less than that from ergotamine by injection, which would be an added point in favour of the former.

The use of ergometrine in this condition is not new and is mentioned in some detail in such a standard textbook as Goodman and Gilman's *The Pharmacological Basis of Therapeutics* (New York, 1940), from which it will be seen that as a form of treatment it has been in use in the U.S.A. for some years now. One reason for the general lack of knowledge by the medical profession of the use of oral ergometrine in migraine may be that most, if not all, of the firms marketing this drug do not mention this therapeutic use in their accompanying pamphlets.—I am, etc.,

London, W.2. H. C. STEWART.

SIR,—It is interesting to notice in your annotation (September 1, p. 538) that there is no mention of urea as a form of therapy. So far as my scanty knowledge of the recent literature exists I cannot recall any reference to urea other than a short note in Dunlop, Davidson, and McNee's *Textbook of Medical Treatment* (1949 edition), where the writer states that it is certainly worth trial. There is no doubt in my mind that it is a very effective remedy, though it can be considered as such only from the very long-term view of prevention of attacks. It is useless for the individual attack, and in my short series of cases I have not been able to follow up the controlled cases for long enough to be able to speak confidently of permanent cure.

The urea is given as 60 gr. in a simple mixture three times daily. The cases are carefully selected, my criteria being chronicity, frequency of attacks, severity of attacks, and failure of other remedies. Thus the history is usually of at least five years' duration, the frequency is at least

once every month, and the severity is such as to cause severe prostration: or, if not, I would say that urea is justified if no relief is obtained from six "veganin" tablets, or similar remedy, within a few hours. Some of my patients have obtained partial relief from ergotamine, but they still complain of the frequency of the attacks. This is ergotamine by mouth: in general practice it is not always practicable to give it by injection.

By using urea continuously I find I can usually get control within a month. The attacks are either less frequent or less severe, or both. After about three months the attacks are so infrequent as to cause minimum trouble. In many patients, after this time, they have ceased entirely. I now gradually taper off the dose until the medicine can be completely stopped. So far my longest period of complete freedom from attacks, and without any treatment, is a year.

At present I am on holiday and cannot refer to my notes, but, speaking from memory, I should say I have treated about 15 patients in this way in the past two years. In every case the response has been excellent: in some cases it seems little short of miraculous. I cannot begin to speculate on the action of urea in migraine, but the fact that it appears to be an empirical remedy does not, to my mind, in the least way lessen its value. How is it that it appears to be so little known? I would say that it is the one remedy that really helps in this distressing complaint.—I am, etc.,

Duffield, Derbyshire. H. S. C. WIGHT.

Referred Pain

SIR,—Dr. J. B. Harman's paper (September 1, p. 521) is of great importance, since it was hitherto widely accepted that local analgesia removed or at least modified referred pain. I would be grateful if you would allow me to ask a few questions. The theory which the author accepts appears to be this: from babyhood onward we explore and gain knowledge of the surface of our body and are therefore in a position to recognize and localize precisely any sensation arising from it. The deeper tissues, however, are unknown to us. Sensations arising from them cannot be placed accurately and are wrongly assumed to come from a surface area supplied by the same segment of the cord. I see two objections to this. First, although a baby in the cot playing with its fingers may be busily correlating visual and tactile impulses, finding out in other words what a certain position of its finger feels like and memorizing this, there are areas of the body (as, for instance, the skin of the back) which we touch only rarely, and yet localization of touch and pain is good. The second point I would like to raise is this. It sounds convincing enough to say that we interpret signals from an unknown part as coming from a well-known one, but is this so? Angina *is* felt in the chest and only secondarily radiates to the arm. What has to be explained is why we experience somatic pain *in addition* to visceral pain.

Professor Cohen's explanation of referred pain assumes that subliminal impulses arise continually in all parts of the body, and that pain from a viscus plus impulses from a homosegmental area may impress themselves on consciousness as pain, where one group alone might remain unnoticed. But does this explain the false localization? Would one not in addition have to postulate a spread from the nerve cells which record pain impulses from the heart to those receiving afferents from the arm? Even then such spread should occur only with severe pain, whereas we find that even a mild visceral pain may have a somatic reference.

Another question: What is tenderness? Is it subliminal pain? Yet a tender area differs from an area which is the site of referred pain. Even the lightest touch on a momentarily painless wound may produce at once a very severe pain. On the other hand, one can handle a limb which is the site of referred pain quite vigorously. I can say from experience that the referred pain produced in mapping out areas of segmental reference (Kellgren) has a peculiar quality. There is something unreal about it, and the reason, I believe, is that when one touches the painful area there is no tenderness.

In cases of injury to the back with pain of sciatic distribution another factor arises. The pain here may be twofold: referred from an injured spinous ligament or caused by the pressure of a prolapsed disk. The latter differs fundamentally because the disk does not irritate nerve endings, it presses on axons. It is as if a telephone wire had been tapped and incoming messages were taken to have come from the end of the line. This, I would say, is a true instance of false localization. Yet this root pain is clinically indistinguishable from referred pain.—I am, etc.,

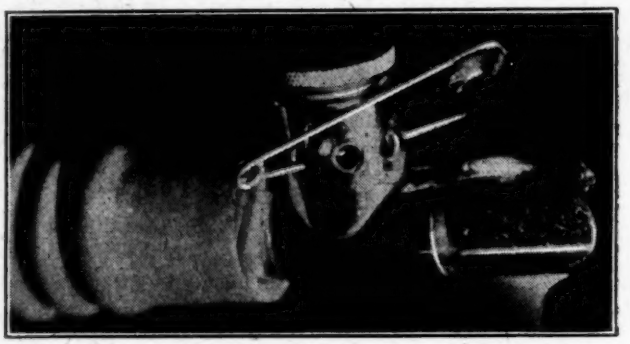
Rotherham. E. G. HERZOG.

Anaesthesia in Children

SIR,—I have given many intravenous thiopentone injections for children and have come to some definite conclusions. In order to attempt an intravenous injection the child must be fairly heavily premedicated, a condition which is not ideal for thiopentone, or in a state of terror, which prevents accurate injection. Further, the veins of a child are small, and difficulty may easily occur in making sure that the needle rests in the vein.

Though the surgeon may cheerfully advise you of the bloodless field in which he is working, I often wonder whether that bloodless field has possibly a direct connexion with the "hovering of the angel's wings" owing to the automatic lowering of blood pressure, and respiratory exchange becoming inadequate.

I suggest an alternative to what, in my opinion, is a hazardous practice. As an Ayre's tube for children of the



6 to 10 group is obviously too small, the alternative is an oral endotracheal tube, following suitable premedication with "seconal" and atropine, and quiet induction by ethyl chloride and ether. What then is to follow? A small child cannot be expected to blow up a rebreathing bag and to exhale through the leaf of the ordinary expiratory valve on the standard Boyle machine. I have therefore thought of an anaesthetic approach which will combine the ideal of a nearly bloodless field, safety to the patient, and the use of a minimum of ether. The expedient is very simple: a safety-pin placed under the teat of the expiratory valve on a standard Boyle machine as shown in the photograph, taken by Dr. V. Magian of the Manchester Ear Hospital.

A slight disadvantage may be the increase in oxygen consumption (a full head of oxygen is necessary, as even the use of a little emergency oxygen may be required to keep the bag from becoming collapsed), but the advantages are minimal bleeding at the time of operation, a healthy patient at the conclusion of the operation, and a lack of post-operative anxiety in the ward.—I am, etc.,

Manchester. H. J. A. SIMMONS.

Sulphamerazine Dangerous

SIR,—In reading the medical journals during the past year or two, and from conversation with those in hospital practice, it has more than once occurred to me that neither doctors

nor pharmacists are sufficiently aware of the latent dangers of the use of sulphamerazine in general practice. An alarming experience which happened to me this week is worth reporting.

While looking after the practice of a colleague on holiday I was called to a girl of 8 years suffering from pneumonia. The onset had been sudden, and the child presented a typical picture of the condition. There was rapid, painful, grunting respirations 40 per minute; the temperature was 101° F. (38.3° C.) and the pulse rate 120. At the left lung base there was diminished air entry and fine crepitations.

I gave 400,000 units of procaine penicillin and issued a prescription for sulphamezathine suspension to be taken 1.5 g. immediately, 0.75 g. every four hours for 48 hours, and 0.5 g. four-hourly thereafter. I had decided to withhold further penicillin, as the child had struggled wildly and appeared terrified of the injection. The mother alleged there had been five previous attacks of pneumonia. I revisited the child in the evening, when she appeared much more comfortable, as was also the case on the next day and the day following that. The air entry to the base improved and the fine crepitations gave way to coarser sounds as the secretion formed and was coughed up. I missed visiting on the fourth morning, but in the evening received a message to say that the child was very much worse. The mother stated that she had started severe abdominal pain and vomiting at 3 a.m. and that this continued throughout the day. By this time nearly 16 g. of the drug had been taken and the fluid intake was said to be plentiful. On inquiry, however, the mother said that the urinary output on the third day was normal, but that since midnight there had been passed only one ounce of urine, and this was heavily blood-stained. The child looked ill and toxic, although the temperature, pulse, and respirations were normal. The lung signs continued to show improvement.

Since its first appearance on the market I have used sulphamezathine in hospital and general practice to the exclusion of all other allied sulphonamides and have never experienced, nor heard of, nor read of, a case of suppression of urine following its use. I at once contacted the chemist who had dispensed the prescription and found that he had, without prior reference to me, substituted "cremomerazine" regardless of its dangers in the dosage prescribed for a child of 8 years.

The child was then seen by Dr. T. Colver, who confirmed the diagnosis and kindly admitted her to his wards at the Children's Hospital. After further haematuria, normal urinary outflow was re-established.

A rapid glance at the back numbers of the *British Medical Journal* shows that such cases are not infrequent.

January 10, 1948. *Correspondence.* Mr. M. D. Sheppard mentioned that he was that week treating his second case of ureteric obstruction due to sulphamerazine crystals.

March 26, 1949. *Any Questions?* An inquirer mentions two cases of anuria following the use of sulphamerazine.

December 23, 1950. J. T. Rice-Edwards reports on a case of sulphamerazine crystals obstructing the urethra of a 13-months boy, and mentions two cases seen in 1950 of ureteric obstruction following sulphamerazine administration.

I know personally of one adult case occurring in this city recently, and have reason to believe that several other cases unreported have been admitted to hospital for relief of partial or complete suppression of urine following sulphamerazine administration.

No doubt in some cases the recommended dose was exceeded by the mother's error or the fluid intake was insufficient owing to the child's resistance, but the fact remains that in the administration of sulphamerazine there is a serious danger which is not shared by other sulphonamides having the same action and giving as good results. I think that the time has come to bring to light some of the unpublished cases of anuria following the administration of sulphamerazine and to query whether its continued use is justifiable when there are safer alternatives.—I am, etc.,

Sheffield. E. C. ATKINSON.

March Fracture in Childhood

SIR,—Dr. Duncan A. Macpherson (August 11, p. 339) describes stress fracture of the metatarsal as being rare in childhood, and this was supported by Dr. Sophia Levin (August 25, p. 497). I venture to suggest that it is merely uncommon and would be found more often if it were kept in mind that the only radiological evidence of fracture may be callus formation after a few weeks. Clinically, the diagnosis is easy: pain in the forefoot without history of injury to that region, localized tenderness over a metatarsal, and a puffy swelling on the dorsum of the foot.

In the last twelve months I have seen four cases confirmed radiologically in this hospital; a fifth case clinically typical but without *x*-ray changes was seen last week. About 13,000 patients are seen yearly in our surgical out-patients, and in this period 25 traumatic fractures of the metatarsals were seen. The ages of my cases are 5, 7, 8, 9, and 10½ years. The youngest patient, the only girl in the series, first developed a stress fracture of her second metatarsal, which was treated in plaster-of-Paris for three weeks. Three months later she returned with a stress fracture of the third metatarsal of the same foot. It is surprising that stress fractures of the metatarsals are so uncommon in children when one considers the frequency of periods of unaccustomed stress, such as at the start of the football season and during epidemics of skipping and hopscotch. It is relevant also that between the ages of 5 and 7 children lose the flat-footed jump of infancy and begin to spring from the toes. This is an important factor in the aetiology of stress fracture of the fibula, a condition of similar incidence in children, a paper on which is in preparation.—I am, etc.,

Royal Belfast Hospital for Sick Children. A. L. GRIFFITHS.

Diagnosis of Trypanosomiasis

SIR,—May I comment on the interesting discussion on human trypanosomiasis appearing in your issues of August 18 (p. 401) and September 1 (p. 546)? In their report of their case Cates and McIlroy state that "repeated blood films were negative." Were these thick or thin films? The distinction is of some importance to those unfamiliar with this disease, as *T. gambiense* is often exceedingly rare in the peripheral blood, especially in cases of long standing. Our routine in the Uganda laboratory included a consecutive daily series of stained thick films for a week or 10 days while the animal inoculations were in progress. An ideal animal for subinoculation is the *Cercopithecus* monkey, which in Uganda was easily obtainable. Our alternative victim, the guinea-pig, was less satisfactory where *T. gambiense* was concerned; it was found expedient to inject several of these animals from each sample of blood in searching for this often unobtrusive trypanosome, and, moreover, to expect a long incubation period. Often with a positive blood one or more animals failed to become infected.

Where glands are palpable, puncture and examination of a series of fresh preparations are, however, the easiest and quickest method available and are especially valuable in village surveys.—I am, etc.,

Cross-in-Hand, Sussex. H. L. DUKE.

Longevity and Cardiovascular Disease

SIR,—I am afraid that the report of my opinion in the Festival symposium on cardiovascular disease in the ageing population (July 14, p. 113) is rather inaccurate. May I be allowed to clarify it?

I demonstrated the drawing of the optic fundus of a lady of 96 years of age, with the arteries lengthened, not shortened, and the veins not nipped by the arteries on crossing (the opinions of some authorities being quite opposite to those facts). I demonstrated also a chart with the diagram of her brachial blood pressure using the palpatory, auscultatory, and oscillometric methods, where her mean blood pressure was normal and a diastolic below 90 mm. Hg; her oscillometer index was equal on both wrists and also on both ankles; her mean pressure on both central retinal arteries was normal and equal (method of Baillart). This healthy state of arterial and capillary circulation, in my opinion, is the explanation of her longevity.

Lastly I mentioned my own formula for measuring the elasticity of the brachial arteries in all cases, except those

of aortic regurgitation—the difference in mm. of Hg between the change of the sound (the diastolic of British cardiologists) and its complete disappearance (the diastolic of Americans) divided by the pulse pressure (first systolic sound and complete disappearance of the sound).

E.g., $\frac{200\ (190)}{70\ (50)}$, therefore elasticity is $\frac{70-50}{150} = \frac{20}{150} = 0.13$.

—I am, etc.,

London, E.1. N. PINES.

Toxic Effect of Proguanil

SIR,—The *Journal* of July 21 reached me to-day, August 15. I have read Dr. P. C. Cosgrove's letter (p. 177) and I cannot but agree that his remarks on the short-term observations of various authors (1945–9) bear little or no relation to the chronic long-term toxicity of proguanil. The bulk of our clinical work in Government and commercial medical service precludes the possibility of a scientific investigation into the problem. This is an easy matter in the U.K., where sorely needed beds for acute cases are occupied by "guinea-pigs" for furtherance of M.D. theses or pseudo-scientific papers.

In my own practice in Sierra Leone I find that I agree with Dr. Cosgrove's findings. He is the medical specialist (Government Medical Service) in Freetown and I am employed by a mining company in the Protectorate of Sierra Leone. Since the introduction of paludrine as a malaria prophylactic among the European employees of the company, I can say that more than an "impressive minority"—rather, an "impressive majority"—of Europeans under my care on the same dosage have made complaint of symptoms exactly similar to those noted by Dr. Cosgrove. However, I would go further and say that employees who were taking mepacrine for three to four years suffered the same symptoms, in addition to the usual criteria of mepacrine toxicity. After relief of symptoms by a change to proguanil the same symptoms recurred in one to two years. These again were relieved by a return to mepacrine.

I have no doubt that, although many people suffer no disability, there are many more suffering from like symptoms, who in view of their disinclination to report sick do not make their views known.

It would appear from my observations that both prophylactics taken for long periods in a hyperendemic area result in similar toxic symptoms, only relieved by a change of the prophylactic drug. In this area (hyperendemic) in non-immune subjects malignant tertian malaria breaks through a prophylactic dose of two tablets of proguanil a day (0.2 g.). Similar findings have been noted in this area with the recommended dose of chloroquine (two tablets of 0.1 g. a week), in agreement with a recent letter (April 14, p. 818) from Dr. J. J. Messent, of the Gold Coast. It has yet to be established that similar toxic symptoms will not be met if the dosage of this drug is increased.—I am, etc.,

Segbwema, Sierra Leone. W. SLATER BROWN.

Blackwater Fever

SIR,—Your leading article (August 4, p. 281) giving an excellent summary of the various theories is of special interest to me as, having once been affected by the fever, as well as having written *Blackwater Fever—Bilious Tertian Malignant Malaria* (1909), I was convinced that blackwater fever was related to the malignant tertian parasite and that this parasite was limited in its area where malaria was endemic, and probably transmitted by a specific mosquito. In spite of the fact that malaria was widespread in an area with thousands of natives it only affected a limited number and apparently in a circumscribed area. Thus, out of 28 tea estates—each with no less than 1,000 natives and others many more—in only one estate did blackwater fever occur. Though a sudden large dose of quinine could produce haemoglobinuria that would be differentiated by the absence of the syndrome signs.

My opinion at that time was that the high degree of liver congestion brought about the sudden destruction of the red cells—in these days one could relate this to the production of a specific haemolysin. With the large-scale destruction of the red cells there would thus be a loss of parasites from the blood, partly from the dehousing of them in the cells. Even if all blackwater fever (malignant tertian) disappeared to-morrow there may be still hyperendemicity from the other malarial parasites, and vigorous malarial control measures would be of importance so long as this did not mean only the giving of antimalarial drugs. In my opinion there should be instituted in the areas concerned measures against the breeding grounds around habitations and the breeding of larvicidal fish for streams. At the All India Sanitary Conference at Simla I took up a large bowl of such fish with mosquito larvae and demonstrated the massacre of the larvae by the fish. A few months ago I saw one of these types at a well-known restaurant at Whitley Bay. The eucalyptus tree, where it can be grown, is an antimalarial measure, as it keeps away mosquitoes, and the oil sprinkled on a handkerchief at the head of a bed is by no means to be despised.—I am, etc.,

Winsley, Wilts. A. G. NEWELL.

Mosquito Bites and Age

SIR,—I would like to make a comment on Dr. R. C. Muirhead-Thomson's article (May 19, p. 1114).

I am in medical charge of a solely European military families hospital. During the last rainy season 28% of all Army children got malaria—only 6% of all Army wives were infected. Admittedly the numbers involved are small—roughly two hundred families—but when it is considered, in addition, that the children concerned are almost without exception under nets between sundown and sunrise it would appear that at any rate here the child is preferred as a source of nourishment by the mosquito.—I am, etc.,

Accra. B. W. HUGHES.

Absence of Appendix

SIR,—Mr. A. L. Deacon's reference (July 14, p. 116) to the probably not-so-rare occurrence of intussusception of the appendix prompts me to report my own experience in this connexion.

In 1942 while at an R.A.F. hospital I saw a case of appendix abscess of some days' duration. I was assured by the patient that his appendix had been removed several years previously, when his abdomen had been opened and drained for peritonitis.

The surgeons had told him it had sloughed away. The abscess resolved with conservative treatment, and he was readmitted after about three months for exploration, as the story of a missing appendix was accepted with a pinch of salt.

At laparotomy I failed immediately to locate the appendix, but palpation of the caecum revealed the truant within. Incision and delivery of the rather attenuated remains of a previously inflamed appendix were satisfactorily completed, and on this occasion I was able to assure the patient that he was leaving hospital without his obsolete but troublesome organ.—I am, etc.,

Eye, Suffolk. J. E. M. BARNES.

Natural History of Venous Thrombosis

SIR,—The paper by Dr. C. Raeburn (September 1, p. 517) is an important and interesting contribution to this subject. The histological evidence which he gives showing recurrent thromboses in the leg veins of a large proportion of the patients he examined post mortem must make us modify our views regarding acute thromboses in individuals confined to bed. Nevertheless, I believe on clinical grounds that his thesis "that in most instances venous thrombosis

in the leg is a chronic additive process and not, as is generally accepted, an acute disorder" requires modification. No doubt it is true of the group he investigated, but this comprised 130 unselected patients, mostly elderly people, who had died in a general hospital. I do not think that he is justified on such evidence in dismissing the possibility of venous thrombosis occurring as an acute disorder.

When venous thrombosis of the leg occurs in younger people a previous history of a long illness is occasionally elicited, but usually there is none. Venous thrombosis following trauma may occur with no immobilization.

A healthy man aged 23, with no previous history of more than trivial illness, while playing hockey was struck on the left leg with a stick. Within a few hours the leg became swollen and painful. When I examined him 24 hours later he had only been in bed for a night's rest. His leg was grossly oedematous and cyanosed, with dilated superficial veins. There was tenderness on deep palpation of the calf. The pitting oedema subsided with the support of elastic bandages and with rest in bed for a few days.

Of 650 patients with leg ulcers, a history of previous venous thrombosis has been found in 521 (80%). The majority were aged 20 to 50 at the time of thrombosis. In 133 of these patients post-partum thrombosis had occurred. While it is possible that some of them might have suffered from previous thrombosis of the legs during illness or other pregnancies or confinements, most of the women had been healthy in the past, and 55 of them were primiparae. It is significant that of the confinements followed by thrombosis only 21% were normal, the remainder being complicated by interference of some kind—for example, the application of forceps, or version—or by retained placenta or severe haemorrhage.

Dr. Raeburn believes that the conception of thrombosis and embolism as surgical complications is false. It is not disputed that immobilization after operation must be an important factor in the cause of post-operative thrombosis, but it is worthy of note that of 26 patients who had suffered from this complication 14 had undergone lower abdominal or pelvic operations and 5 inguinal herniotomy. This last operation does not usually require prolonged immobilization. It would seem that trauma may have played a part in the cause of these thromboses, which appeared to be acute, though information about possible previous thromboses is lacking except that there was no history suggesting such.

The figures relating to post-operative venous thrombosis and embolism given by E. V. Allen, N. W. Barker, and E. A. Hines (*Peripheral Vascular Diseases*, 1946) support the view that not only immobility but also injury to veins and infection are important factors; that the operation plays a part as well as the immobility of the lower limbs following it.

Though Dr. Raeburn has shown that in old people who are immobile venous thrombosis is a chronic additive process it would seem that acute venous thrombosis may occur in younger persons, especially when related to trauma and infection.—I am, etc.,

Leeds. S. T. ANNING.

Breakdown of the "Healed" T.B. Lesion

SIR,—It is apparent to all mass *x*-ray workers engaged in the fight against tuberculosis that a considerable number of persons, in all countries, contract tuberculosis at some period of their lives. On the *x*-ray film of the normal individual this condition is usually indicated by various small opacities—referred to as "healed lesions." But these so-called healed lesions can, and very often do, break down after *x*-ray examination—with unfortunate results. According to Frost (1939) and Springett (1950, 1951) the highest breakdown rate occurs in young adults (15–24) of both sexes, with a gradual decline in the rate to the age of 60—where it is below 1 per 1,000 examined.

As routine mass *x*-ray examination of younger sections of a population extend, it is appreciated that the number of breakdowns, following upon a "normal" miniature film, will greatly increase. For example, in one year's working at the anti-tuberculosis centre of the World Health Organization in Istanbul, with almost 50,000 miniature film examinations, we have encountered 25 such breakdowns. Although this number (0.05%) may appear insignificant, it means that within the past year the centre has been criticized 25 times for informing an individual that his condition is normal—and shortly afterwards he has developed a clinically significant lesion.

As the plan is extended to other units, we anticipate a corresponding increase in the number of criticisms aimed at our work, which, apart from its immediate adverse effect, also leads to some difficulty in persuading the population that mass *x*-ray examination has any value. In dealing with this problem we now recommend that any individual with a healed lesion should return to the centre (or his nearest tuberculosis dispensary) every three months for a further miniature film examination. In this manner we aim to prove the value of mass radiography, in that we can inform a person that he has had a previous tuberculous infection, which is now quiescent, but that he should report for a check-up at frequent intervals—not only in his own interest, but also for the sake of his family.—I am, etc.,

Istanbul. CECIL ASHWIN,
World Health Organization.

REFERENCES

Frost, W. H. (1939). *Amer. J. Hyg.*, **30**, Sect. A, 91.
Springett, V. H. (1950). *J. Hyg., Camb.*, **48**, 361.
—— (1951). *British Medical Journal*, **2**, 144.

Hepatic Coma

SIR.—Dr. E. D. H. Cowen's suggestion (August 4, p. 277) that all cases treated by the Latner regime should be reported to the medical press prompts me to record the following case of hepatic coma.

The patient was a married woman aged 44 years. She was admitted to hospital on October 11, 1950, with jaundice. Three weeks prior to admission she had felt unwell, with aching in her limbs and diminished appetite. She had not noticed any change in the colour of her urine or faeces. One week later a friend told her that her eyes were yellow. During the past two weeks the jaundice had become generalized and deeper and her malaise and anorexia had improved. She had no abdominal pain and no history suggestive of cholecystitis or previous biliary colic. No history of recent injections was obtained.

She was a well-nourished woman who, apart from her deep jaundice, looked and felt well. There was no finger clubbing or skin petechiae. The liver edge was palpable two fingerbreadths below the costal margin. The spleen was not palpable, and examination of all other systems was negative. A diagnosis of infective hepatitis was made. Liver function tests (October 12, 1950) were as follows: serum alkaline phosphatase, 13 units/100 ml.; serum bilirubin, greater than 5.6 mg./100 ml.; thymol turbidity, 7.0 units; thymol flocculation, ++; colloidal gold, 4; gamma globulin, 0.69 mg./100 ml.

A full blood count on October 12 showed erythrocytes 3,680,000 per c.mm., Hb 9.8 g./100 ml., W.B.C.s 10,000 per c.mm. (polymorphs 76%, lymphocytes 18%, eosinophils 2%, basophils 1%).

A straight *x*-ray picture of her abdomen showed no opaque masses. The patient remained well with no change in her jaundice until October 17. During this time she had been receiving a low-fat and high-protein diet, with vitamin K parenterally. On October 17 she became somewhat drowsy and her breath was noticed to have a foul odour. In view of this sudden lapse into semi-coma it was decided to start her on Latner's therapy. Her blood urea at this time was 20 mg./100 ml.

The following day her condition had deteriorated and she was completely comatosed and restless, necessitating the administration of paraldehyde. She developed numerous cardiac extrasystoles, and a triple rhythm and systolic murmur were heard at the apex. Blood pressure 120/80. Blood urea 26 mg./100 ml.

On October 19 her liver edge was no longer palpable and she was much worse. On October 20, after being on Latner's therapy for three days, she died. Liver function tests carried out on October 19, two days after starting Latner's therapy, were as follows: serum alkaline phosphatase, 20.2 units/100 ml.; serum bilirubin, 208 mg./100 ml.; thymol turbidity, 4 units;

thymol flocculation, +; colloidal gold, 3; gamma globulin, 1.57 g./100 ml.; serum protein, 7.4 g./100 ml. (albumin 4.5 g./100 ml., globulin 2.9 g./100 ml., A/G 1.55). Agglutination tests for leptospiral infection were negative, but a Wassermann reaction taken on October 14 was strongly positive.

At necropsy the liver weighed 780 g. and was much reduced in size. The surface was uneven, showing many small raised yellow areas with intervening red sunken areas. On section the bulk of the liver consisted of these yellow areas separated by small amounts of reddish tissue. The bile ducts were patent and the gall-bladder was healthy. The spleen weighed 170 g. and was quite firm. The kidneys were bile stained but with normal architecture. Many lobules were entirely replaced by pale-staining tissue-containing blood vessels and proliferating bile ducts. Other lobules had retained their normal architecture, but some cells showed degrees of degeneration. Most liver cells appeared to have developed as the result of regeneration with imperfect reconstruction of the normal lobule architecture. Sections of the kidney showed the presence of bile casts but no gross tubular damage.

Although the patient died the liver contained a large amount of surviving and regenerated hepatic tissue and seemed correlated with the second group of liver function tests on October 19, which did not give any indication of further parenchymatous damage, although the obstructive element seemed to have increased.

Comparison of this patient's liver with that of a previous case which had run an almost similar course is interesting. This patient was a girl aged 27 who developed jaundice two weeks after a normal pregnancy. Two weeks after the onset of the jaundice she lapsed into coma, and on admission the liver function tests were: serum alkaline phosphatase 9.7 units/100 ml., serum bilirubin 6.2 mg./100 ml., thymol turbidity 10.0 units/100 ml., thymol flocculation +++, colloidal gold 5. This patient, who was not treated on Latner's regime, died two days after admission. Histology of the liver in this case showed the complete absence of any hepatic cells.

Conclusions from this case are difficult, but it was felt that the therapy given may have been responsible for the large amount of surviving liver tissue which was found post mortem.—I am, etc.,

Chilwell, Notts. S. SHUBERT.

Adrenaline Cream in Rheumatism

SIR,—"Committees of men never created anything." I have little experience of this method of therapy and have no decided opinion one way or another about its efficacy, but would point out a logical conclusion which appears to arise from the discussion (July 14, p. 120, and July 28, p. 236) in the *Journal*. Howell, using a control cream, produced some relief in 16 cases out of 20 (80%); Bywaters *et al.* produced some relief using an identical cream in 72 trials out of 286 (only 25%). Had the two experiments been similar the chances of this difference occurring are remote, less than 1 in 1,000. It seems probable, therefore, that the methods adopted by Bywaters *et al.* must have differed from those of Howell; and if they wish to use the statistical method to refute Howell's claims they must either increase the sensitivity of their methods of detecting and/or producing relief of pain, so that they are comparable with Howell's, or increase the number of trials they have made.

The use of the χ^2 test is, of course, impressive; but, unless an experiment conforms to the common-sense logic I have pointed out, no importance should be attached to statistically negative results.—I am, etc.,

London, W.1. GEOFFREY E. LOXTON.

Courses in Public Health Engineering

SIR,—I was most interested to read the article on public health engineering by Dr. R. F. Guymer (August 25, p. 472). It may be of interest to your readers to know that a similar course was instituted in the Department of Civil Engineering, University of Durham, last October and has been running successfully for the year. It is a one-year postgraduate course designed to supplement the undergraduate studies in the physical sciences with a grounding in the biological sciences and an introduction to the ideas and methods of medicine in the field of public health. With the co-operation of the appropriate departments the lecture and laboratory programme includes elementary plant biology, freshwater biology and algology, applied bacteriology, public health, planning law, and statistics; the applications of these subjects to engineering are covered in the lectures on public health engineering.—I am, etc.,

Newcastle-upon-Tyne. PETER C. G. ISAAC.

POINTS FROM LETTERS

Anatomical Atlases

Professor H. A. HARRIS (Cambridge) writes: Since my letter (July 21, p. 178) my attention has been drawn to the fact that the incorrect diagram in Gray's *Anatomy* was corrected in the 28th edition, 1942, and the mandibular branch of the facial nerve is now shown in its usual course.

Hirschsprung

Dr. T. PEARSE WILLIAMS (London, W.1) writes: May I make a slight correction to a statement in Mr. Denis Browne's helpful letter on megacolon (September 1, p. 546)? Harald Hirschsprung (1830–1916) was not a surgeon, but was appointed professor of children's diseases at Copenhagen in 1877. His first report on the condition was a paper read at Berlin on two pathological specimens with a full case report. This is the paper usually referred to. I have been able to trace only two further publications by Hirschsprung on megacolon—in 1890 and 1891. He wrote also on occlusion of the oesophagus in the newborn, intussusception, rickets, and rheumatic nodules.

Toxic Effects of Proguanil

Dr. LUCRETIA H. BYRNE (London, S.W.16) writes: My experience has been the same as Dr. C. S. P. Hamilton's (September 1, p. 547). I used proguanil for over three years extensively for malaria and as a suppressive, and I cannot remember any case showing definite toxic effects.

Primary Control

Dr. MUNGO DOUGLAS (Bolton) writes: In connexion with my letter, "Use of the Self" (August 18, p. 420), I would like to explain the term "primary control." It is the name given by Mr. F. Matthias Alexander to a principle which demonstrates its manner of operation to a person who employs the Alexander technique. It influences the self as a whole, so that at one and the same time the head goes forward and up, the neck is relaxed, the back lengthens and widens, and the parts which may be described as the upper and lower arms, the hands, fingers, and thumbs, the upper and lower legs, the feet, and toes diverge in the greatest possible degree from the parts to which they are joined and thus immediately related. The employment of the technique enables the person to experience this manner of direction and teaches him how he may consciously guide the self as a whole in the same manner. As a consequence he is enabled to control the relativity of all the parts in the manner described, and to provide himself with a total self in which the muscle tension throughout is the least possible. In such a self the mechanisms of sensory appreciation are adjusted in the best possible way and, therefore, in a way which enables him in his use of the self to appreciate, assess, and learn the manner in which he may best guide movements which he desires to perform. His reaction to living is made up of his movements, and a person who guides his movements in the best possible way may be said to react in his living in the best possible way.

Teaching Value of a Scientific Film

Mr. MALCOLM DONALDSON (London, W.1) writes: Every young teacher of medicine should study the excellent article on films by Miss Hannah Steinberg and Dr. H. Ellis Lewis (August 25, p. 465). . . . The best method of using films as an aid to teaching medicine has still to be worked out. It may well be that different types of lectures need different techniques, but most people will agree that the half-hour elaborate films have only a limited value. . . . It seems to me there are great possibilities in having viewing machines for short bits of films which the student can study at his leisure.

Obituary

J. M. WOODBURN MORISON, M.D., F.R.C.P.Ed. D.M.R.E.

Dr. J. M. Woodburn Morison, formerly professor of radiology in the University of London and director of the radiological department of the Royal Cancer Hospital, died at Bexhill-on-Sea on September 3, aged 76.

John Millar Woodburn Morison was born in Beith, Ayrshire, and educated at Ayr Grammar School. He studied medicine at the University of Glasgow, where he graduated M.B., C.M. in 1896. Shortly afterwards he went into general practice in Manchester, a step which he never regretted, for after he became a specialist this early experience lent much to the value of his teaching. It was during the first world war when he was serving in India that he was introduced to *x*-ray work. Later he went to Liverpool and worked with Thurstan Holland, with whom he formed an enduring friendship. In 1924 he obtained the D.M.R.E. of Cambridge and also proceeded to his M.D. degree. A year later he took the M.R.C.P. of Edinburgh and was elected a Fellow in 1929.

After a short period in partnership with the late Dr. Alfred E. Barclay in Manchester, Woodburn Morison was invited to take charge of the new *x*-ray department in Edinburgh which was opened in 1925. Here he organized one of the earliest of the courses for the diploma in radiology. In 1930 he was appointed to the first chair of medical radiology to be founded in this country—that of the University of London. It was tenable at the Cancer Hospital, and Woodburn Morison was some years later appointed to be director of radiology at that hospital. He retired during the second world war, but he remained fully occupied throughout the war, working for the E.M.S. For many years he had delivered a course of lectures at Cairo University, and latterly he had been spending much of each winter living in Alexandria, where he was visiting professor of radiology at Farouk University.

Many honours were awarded to Woodburn Morison during his professional lifetime. He was president of the radiological section at the Annual Meeting of the B.M.A. in Edinburgh in 1927, and he later became president of the electrotherapeutic section of the Royal Society of Medicine. A past president of the British Association of Radiologists, he was an honorary member of nearly all the important foreign radiological societies. He published many papers on his specialty in this and other journals.

J. B. K. writes: Woodburn Morison was one of the big figures in radiology over the period of its most active development, and before the present sharp division into diagnosis and treatment. He did much for the British Institute of Radiology, the Radiological Section of the Royal Society of Medicine, and was a president of the Association of Radiologists, which preceded the present Faculty of Radiologists. Few men can have taken a more active part in the development of their specialty. Only as recently as the International Congress in London last year Woodburn Morison was to be seen as upright, clear-eyed, and smiling as ever. Large in stature and personality, Woodburn Morison was a charming companion with wide interests. He had read and travelled extensively, and had many friends among his colleagues on the Continent. He was a really fine teacher, and many radiologists both in this country and abroad who were his pupils will long remember him with the greatest respect and affection.

G. DOUGLAS ROBERTSON, F.R.C.S.

Mr. G. Douglas Robertson, formerly senior surgeon to the department for diseases of the ear, nose, and throat at St. Mary's Hospital, died in the Royal Hampshire County Hospital, Winchester, on August 7 after a brief illness. He was 59 years of age.

Granville Douglas Robertson was the son of Lieutenant-Colonel Robertson, of the I.M.S., senior physician to the General Hospital, Madras. Educated at Charterhouse School, he entered St. Mary's Hospital medical school in 1909. Shortly after qualifying in 1914 he joined the R.A.M.C., serving throughout the first world war. After the war he returned to St. Mary's to become house-surgeon to the late Mr. V. Warren Low, and subsequently to hold the position of surgical registrar. He obtained the F.R.C.S. in 1923. His first staff appointment at St. Mary's was in 1928, when he became supernumerary assistant surgeon to the ear, nose, and throat department. Three years later he became assistant surgeon, and in 1938, on the retirement of Mr. Cecil I. Graham, he moved up to senior surgeon. Being in the Regular Army Reserve, he was recalled to active service at the outbreak of hostilities in 1939, and served throughout the war, being among those evacuated from St. Nazaire. Robertson also held appointments at the Paddington Hospital, the Princess Louise Kensington Children's Hospital, and Wembley Hospital.

Robertson was a very sound E.N.T. surgeon. He took his share in committee work and was for a period chairman of the medical committee at St. Mary's Hospital. Soon after his return from the last war he decided to seek early retirement in the country, and in 1947 he left St. Mary's and London to live at Itchen Abbas, near Winchester. On his retirement he was elected to the consultant staff at St. Mary's.

"Duggie" Robertson possessed great charm of manner and outstanding good looks. He was popular with his patients, colleagues, and students alike, always ready to come to emergencies and to proffer help to anyone in trouble. Happily married, he leaves a widow, to whom all his friends and colleagues extend their sympathy.—J. F. S.

G. GREY TURNER, M.S., F.R.C.S.

Mr. Norman Hodgson writes: Having had the unique privilege of being associated with Professor Grey Turner for twenty years at the Royal Victoria Infirmary, Newcastle-upon-Tyne, and during that time of acting as his assistant in private practice, I would like to add my own personal tribute to the memory of this remarkable surgeon and to record my gratitude for a friendship which continued to the very last by correspondence and contact at our hospitals, surgical societies, and homes. His achievements have been recorded by others, but none can appreciate more than I the enormous amount of unremitting toil he gave to his craft, which enabled him to reach the heights he attained. Speaking of a surgeon's training, he liked to quote the words of William Hunter: "Were I to make a man truly great in his profession,

I would place him in a large hospital where he might attend the sick and dissect the dead." This was the spirit in which Grey Turner worked.

In the Royal Victoria Infirmary each week he had two operating sessions, which, commencing at 10 a.m. and lasting late into the afternoon, were sustained by cups of tea of a special brew. In addition he held a weekly out-patient clinic and paid almost daily visits to his wards. Frequently he would return in the late evening to visit a patient whose progress gave cause for anxiety. To all this was added a private practice filling a large private hospital. His record-keeping, preparation of papers, and lectures kept him at his desk until the early hours of the morning.

In the nineteen-twenties he did a great deal of operating in patients' own homes, often in remote parts of Northumberland, which could be reached only after a long journey by car. He always had in readiness at his house what was called "the emergency bag," armed with which he was prepared at the shortest notice to answer any call and perform operations of a magnitude which to-day are undertaken only with all the resources of a modern hospital. How successful he was in this work is evidenced by the praise given to this day by the country doctors of his native county. At the private hospital was a pathological museum in which every "specimen" removed at operation or post-mortem examination was preserved and catalogued. If it can be called a hobby, this museum was Grey Turner's recreation. No effort was too great to obtain the after-history of his patients or to secure a post-mortem examination. It is a great tribute to the loyal co-operation of his practitioner friends that they kept him constantly informed of the progress of patients. A typical instance was the message received from a practitioner that a patient on whom Grey Turner had performed an oesophago-gastric anastomosis—his first successful case—had been accidentally killed in a town 20 miles from Newcastle. Together we went late at night to the hospital in which the man died and returned in sober triumph with the "specimen" to add to the collection.

His method of lecturing was characteristic—lantern slides, specimens, and patients all blended to present the complete picture—and he never omitted the historical background or a tribute to a pioneer. We in Newcastle are happy to remember the last two such demonstrations he gave: one in March this year to the members of the Moynihan Chirurgical Club, of which Grey Turner was the last surviving founder-member, and the second in May, when the Infirmary celebrated its bicentenary. On this occasion he was surrounded by friends and patients and was delighted by the warmth of his reception. He loved the "Old Infirmary," doomed now to be demolished, and talked most affectionately of the personalities associated with it. He had the same love for the medical school, and in 1934 wrote in collaboration with his friend Dr. W. D. Arnison *The Newcastle-upon-Tyne School of Medicine, 1834–1934*. The sisters in his wards and operating theatre—the latter being that used by his teacher, Rutherford Morison—were his devoted allies, and he in turn was liberal in acknowledging the part they played in the success of his work.

It is difficult to believe that we will never again meet Grey Turner on the corridor of the Infirmary, but the example he set will remain a stimulus to generations of surgeons in the Newcastle school of medicine.

Mr. McNeill Love writes: May I be permitted a few lines in appreciation of Grey Turner's work on active service? I had the privilege of being his assistant throughout practically the whole of his overseas career in Mesopotamia, and I know that this part of his life's work was one of his most treasured memories. I first met Major Grey Turner in June, 1916, shortly after the arrival of the 32nd British General Hospital at Basra. He was drinking large quantities of tea from an enamel mug, and writing notes on the cases he had seen that day in a ledger he had acquired from the Q.M.'s store. At that time heat stroke was enemy No. 1, and I often assisted him in dragging from the corrugated covered sheds in which the sick were housed unconscious patients with hyperpyrexia, so that they could be douched with water drawn from a nearby canal by Arabs. This was their only chance, and some survived. In the autumn the hospital was transferred up-stream to Amara, and was soon flooded with wounded from the unsuccessful attempts to raise the siege of Kut, and for some three months nearly every hour of daylight (and an occasional one by lamplight) was occupied in dealing with grossly infected wounds, secondary haemorrhage, and amputations. When Kut was eventually captured by the Turks the work of the hospital temporarily dwindled, so concerts and sports were arranged in order to relieve the boredom of the personnel. "G. T." realized their value in maintaining morale and was an ardent supporter of these amusements. In order to stimulate interest in sports he himself entered for the 100 yards. When nearing the tape he suddenly "cracked," and that evening he called me into his tent: he had torn some of the upper fibres of the right quadriceps muscle, and already there was a large effusion above the knee. "Fascinating," he said, "how quickly blood can suffuse through the tissues."

In the summer of 1917 Sir Victor Horsley visited the hospital, only to die of heat stroke a few hours later. This was a great shock to G. T., and as we marched in the funeral procession to the desert grave he spoke very feelingly of Horsley's achievements, and of the loss to British surgery which was occasioned by his untimely death. Soon afterwards G. T. developed an obscure abdominal condition which he thought was probably recurrent subacute pancreatitis. In any case it was obvious that even his boundless energy had been sapped by long bouts of overwork, often in exhausting conditions. Reluctantly he was invalided home, but he bequeathed to the hospital a tradition of zeal and self-sacrifice which long remained a beacon and an inspiration to those who were left to carry on his work.

J. L. B. writes: The passing of Professor Grey Turner brings to mind scores of memories. Two stand out. I recall when we were very "hospital minded" being shocked when he allowed so many infants, after operations such as those for cleft palate, to be given to the mothers' welcoming arms outside the operating theatre and taken home. I, for one, was often aghast that children should be discharged so early; but they did remarkably well. Grey Turner had a great regard for the home and economic welfare of the patient. I well remember a man who had an accident on his arm and whose operation was certainly not in accordance with textbook teaching. The result was anatomically almost grotesque, but the man could do his particular job far better than an orthodox operation would have allowed. Grey Turner looked ahead, and obtained so often not merely a "surgical" cure, but a social and "occupa-

tional" cure—fitting men for normal life. A generation ago it was not so popular as it is now to think of the home, social, and economic background of men's lives, but in these ways Grey Turner was years ahead of his time.

GEOFFREY EVANS, M.D., F.R.C.P.

Dr. J. E. S. Stephens writes: Abler pens than mine will write well-deserved tributes to the late Dr. Geoffrey Evans, but I think the following little story of an incident which occurred nearly 25 years ago in Bart's medical out-patients worthy of record. Geoffrey Evans had an unusually obtuse patient up one morning, and had asked every conceivable question about his history and complaint, receiving a dull response of, "No, Sir," to each. Finally he said to the patient, "Have you a pain?" Back came the inevitable, "No, Sir," Geoffrey Evans looked at him and as quick as lightning said, "Well, tell me where your pain would be if you had one." The patient pointed to his gall-bladder region, and from that the necessary investigations were instituted.

Evans had a marvellous understanding of patients as human beings rather than specimens of disease, and inevitably inspired confidence. His teaching, while perhaps dogmatic, was always clear and incisive. After all these years I can still quote some of his ward rounds verbatim, which demonstrates his great personality.

Dr. GEORGE ALAN SIMMONS died at Tydehams, Newbury, on July 28, aged 71. He was the eldest of four brothers, sons of the late George Simmons, of Addlestone, Surrey, and was born there in 1880. After his schooldays at Bradfield College, where he was in the winning team for the Ashburton Shield, he went up to Christchurch, Oxford, and thence to the medical school of St. Thomas's Hospital. After qualifying in 1907 he held resident appointments at the Victoria Hospital for Children and at St. George's Hospital. For a time he was in practice in Bayswater. After that, in 1914, he joined the late Dr. W. D. Coplestone in partnership at Newbury, in which town he practised until his retirement in 1948. During the 1914–18 war he served with the R.F.C., as it was then known. Returning to Newbury, he undertook much public activity as well as working hard in a busy practice; he was medical officer to the dispensary, anaesthetist at the Newbury Cottage Hospital (now the District Hospital), and medical officer at the infant welfare clinic and at the Poor Law Institution. He had many interests outside his purely professional work—notably in promoting and directing the development of the Tydehams estate for housing purposes, where his own house, "Crowsteps," struck a note of novelty and ingenious planning unfamiliar at the time but now by no means unusual. He was a very fine figure skater, had been a notable long-distance runner both at Oxford and at St. Thomas's Hospital, and early became a keen motorist. He was associated with A. V. Roe in his pioneer aviation construction. In 1910 Dr. Simmons married Winifred, daughter of the late Samuel Berger, who survives him with their three sons, of whom the eldest, Dr. Michael Simmons, is a partner in his father's old firm.

Dr. DOUGLAS HAY SCOTT died on August 3, aged 60. Educated at Dundee High School, he went on to University College, Dundee, with a scholarship. He graduated M.B., Ch.B. in 1914 after a brilliant student career. At one time he was editor of the university magazine. During the first world war he served in the R.A.M.C. with the Highland Division, retiring with the rank of major. After working for a time as assistant to the professor of physiology at Dundee, he went into practice in that town. There he led a very active life, being a member of the local panel committee and holding a number of outside appointments, including that of tutor in clinical methods at the Dundee Royal Infirmary, lecturer in vaccination at St. Andrews University, and county director of the British Red Cross Society. He took a special interest in asthma and industrial medicine, on one occasion addressing the Scottish Insurance Institute on the subject of "The Injured Worker." In 1928 he came to London to devote himself to asthma research. At this time he was contributing many articles and short stories to various publications, and when a vacancy was advertised in 1930 for an assistant editor on the staff of this *Journal* he applied for the post and was appointed. After a year, however, he decided to join the medical department of a publishing firm. During the last 20 years he saw many important medical works through the press, and he was himself part-author and editor of several textbooks for nurses.

Dr. ERNEST WALTERS PRICE died at his home in Narberth, Pembrokeshire, on August 5, aged 74 years. The eldest son of Dr. Hugh Price, of Narberth, he completed his training at St. Bartholomew's Hospital, qualifying M.R.C.S., L.R.C.P. in 1901, and subsequently practised in Narberth for 48 years. His practice was large, and in his early days Dr. Price travelled to his patients in this scattered rural area on horseback or driving his trap. With the coming of motor-cars he became an enthusiastic motorist, and took much pride in his cars. For many years he was medical officer of health to Narberth and also medical officer to the G.P.O. He founded the Samaritan Cupboard Fund in Narberth before 1914, and the good work of assisting necessitous cases is still carried on. He was lecturer and examiner to the St. John Ambulance Association. One of the senior practitioners in the county, he was an able physician and keen diagnostician, deeply interested in all his cases. Kindly and tolerant, he had an encouraging word for all men, and a cheerful smile and youthful enthusiasm for all things that came his way. In his younger days he captained the Narberth rugby team, and his love of sport—particularly of horses and the hunt—continued throughout his life. He was a fine horseman, hunting with the South Pembrokeshire Hunt, and he exhibited at agricultural shows. He was a great and outstanding personality with all the virtues of the family doctor, a type that is fast disappearing from our social life. He will be sadly missed by his colleagues and all classes of the community, and the sympathy of all will go out to his family, who devotedly nursed him in his last illness.—A. B. D.

Dr. COLIN BOSTOCK BYRD, one of the best-known doctors in Westmorland, died suddenly on August 10 at his home in Glenridding, aged 58. In the 1914–18 war he enlisted as a private in the Coldstream Guards, was severely wounded in France in 1917, and was invalided out of the Army. He then took up the study of medicine at Liverpool University, qualifying M.R.C.S., L.R.C.P. in 1922. After holding various hospital appointments he settled in Glenridding, Ullswater, following the late Dr. Moon. He took a keen interest in local affairs, was fond of music and drama, and wrote a number of plays, several of which were successfully published. Universally respected, he was a guide, philosopher, and friend, and a tower of strength to the community. Dr. Byrd took an active part in local medical affairs, and was a loyal supporter of the B.M.A., representing Westmorland at the Annual Representative Meetings from 1943 to 1947. His sane and wise counsel will be sadly missed. A keen and expert fisherman, he could tie a beautiful fly. He was the finest type of country practitioner, and there is no better man. He leaves a widow, a daughter, and a son.

Dr. PETER BOYLAN, of Walthamstow, London, E.17, died at Whipps Cross Hospital on August 14 after an operation. He was 55 years of age and had been in poor health for some time. Born in County Sligo, he graduated M.B., B.Ch., B.A.O. from the National University of Ireland in 1920. He had a brilliant record as a student, qualifying in the minimum possible time. He first practised as an assistant in general practice at Shifnal, Shropshire, and in 1928 secured his own

practice in Walthamstow. He proved himself to be a conscientious and hard worker and took a deep interest in local medical affairs. He joined the B.M.A. in 1920 and later became an active member of the South-west Essex Division, of which he was chairman in 1936–7. He represented the Division at the Annual Representative Meeting held in Dublin in 1933. For many years he was a member of the Essex Panel Committee and its more recent counterpart, the local medical committee. He took a deep interest in the treatment of the poorer members of the community, and in the middle 'thirties, with the late Dr. Panting, he was instrumental in arranging with the county council a new scheme whereby free choice of doctor became available for public assistance patients in the Walthamstow area. This was probably one of the first schemes of its kind in the country and proved to be very successful. He was chairman of one of the local medical boards and was medical referee for the Ministry of Labour as well as being referee for some assurance societies. He leaves a widow and two children, both of whom are now studying medicine. To his wife, who is carrying on his good work in the practice, we extend our deepest sympathy in her tragic loss.—P. G.

DR. CHARLES DAKING CARDINALL died at Hatfield on August 17, aged 82. He received his medical education at St. Bartholomew's Hospital, and qualified M.R.C.S., L.R.C.P. in 1893, in which year he also took the L.S.A. He carried on for many years a busy general practice from Church Road, Willesden. In 1915 he was appointed honorary anaesthetist to Willesden General Hospital, a post which he held till 1934, when he was appointed honorary consulting anaesthetist to the hospital on his departure from Willesden to become a partner in a general practice at Hatfield. After the death of his partner he carried on the practice alone, and during the war years had a very strenuous time, for in addition to his practice he was medical officer in charge of civil defence casualty services, and he also acted as M.O.H. In 1946 he had a severe illness and did not regain his former vigour and activities. Dr. Cardinall was most conscientious and showed a high sense of duty in the performance of his work at Willesden General Hospital, both as an anaesthetist and in his attendance at committee meetings. He never allowed his hospital sessions to be interrupted by other calls, and he did much emergency work. In his youth he was a keen athlete and tennis player, and he took a great interest in the latter game all his life. He was very quiet and unobtrusive in manner, but shrewd and penetrating in thought, with a kindly and humane outlook which made him a most valued colleague. He was married, and leaves a widow and two married daughters.—W. M. D.

DR. WILLIAM PENNINGTON GRELLET died on August 22 at his home in Hitchin, Hertfordshire, at the age of 76. He was educated at Bedford School and Guy's Hospital, qualifying in 1901. His father, Dr. Charles Grellet, practised in Hitchin before him, and after qualification "Dr. William," as he became known, joined the practice and remained in it for 50 years. During this time he saw many changes, but he always managed to adjust himself to them, whether it was the unreliability of the earliest motor-cars or the upheaval that followed the introduction of the Health Service. He was one of the first panel doctors, and his "family club" for those who could not afford anything else was a great boon to the poor: at 6s. a year, for all treatment and medicine, it was of course a financial loss, especially as it was not unknown for the patient to discover 5s. left on the dressing-table after Dr. William's visit. For 37 years he served upon the general-practitioner staff of the North Herts and South Beds Hospital, an appointment which he enjoyed to the full, and no matron ever had the courage to tell him that his patient could not be admitted. It was his invariable practice to assemble an entire family before an operation to explain everything in detail to them, and he would repeat the process afterwards, when he would deliver his awe-inspiring prognosis. So great was his clinical judgment that he was seldom wrong. This was typical of the way in which he gained the love and confidence of his patients, and even when a consulting surgeon was called in the patient's only worry was that "Dr. William" should be there too. And of course he always was. For 25 years he was police surgeon to the Hitchin district, and his commanding appearance, his emphatic gestures, and his curious habit of repeating himself made him an impressive figure in the witness box with whom few juries dared to disagree. By the time the National Health Service had taken control of his old hospital he had retired. Although he accepted the change as inevitable he seldom commented on it, but it was clear that he deeply regretted the passing of the old days and the family doctor, of which he himself was such a wonderful example. His practice was essentially a personal one, and the district has lost a man of great kindness and ability who was held in high esteem by his patients and his colleagues. Few men can have given so much to general practice. It was, in fact, his whole life, and it seemed that he could not accept the loss of his work. Ill-health overtook him, and he was given very little time to enjoy his brief retirement. He is survived by his widow, to whom we express our deepest sympathy.—D. W. J.

Medico-Legal

DOCTOR ATTENDING DOCTOR

Claim for Fees Dismissed

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

The circumstances in which one doctor is entitled to charge another for medical attention were discussed in an action recently brought in the Dublin High Court[1] against the executors of Dr. Cyril Bradlaw by Dr. Jacob Robinson, of Dublin. Dr. Robinson claimed fees of 2,000 guineas for attending Dr. Bradlaw from December 24, 1946, until December 14, 1949, when he died. Dr. Robinson's case was that Dr. Bradlaw suffered from heart trouble, and was visited almost every day, and sometimes two or three times a day. Dr. Robinson gave him many inhalations and injections, and it was probably due to his treatment that, while he might have dropped dead at any time, he lived for nearly three years.

The defence was that no money was due because whatever treatment had been given was given voluntarily from one doctor to another, and that in any event the amount claimed was exorbitant.

Dr. Robinson said that when Dr. Bradlaw first consulted him he was breathing heavily and suffering from heart trouble, for which he said other doctors had given him up. He was a squat sallow man weighing about 22 stone. He had been a ship surgeon for 15 years, and on returning to Ireland he had practised very little, if at all, but had lived with his wealthy mother on an allowance from her of £7 a week. Dr. Robinson said that Dr. Bradlaw had often mentioned payment, and that if his mother died before him he would amply repay him for his services, but if he died first the account was to be sent to his mother. In fact the mother died first, and Dr. Bradlaw, whose condition was considerably worsened by his mother's death, died shortly after. It was not Dr. Robinson's practice to send in a bill until a case was finished or he was asked for it, and he never sent Dr. Bradlaw a bill or received any fee from him.

In cross-examination Dr. Robinson said that most of the visits were charged at his maximum rate of two guineas because Dr. Bradlaw was not a practising doctor, although he had been one until he became too ill. It was the practice that one doctor should not charge another, but that did not

1 *Irish Times*, July 24.

mean he could not if he wanted to. Dr. Bradlaw had given him presents from time to time, including a very good watch, but these were not in consideration of the trouble given as a patient.

Evidence was given by Dr. Bouchier Hayes, Mr. Frederick Gill, Past President of the Royal College of Surgeons, and Dr. Joseph Patrick Brennan, president of the Guild of Catholic Doctors. It was the practice and the recognized etiquette of the profession that a doctor never charged a doctor, or the widow or children of a deceased doctor, or a nurse before marriage, for medical attendance. If, however, the money with which the fees if charged would be paid was clearly not made by the practice of medicine, there was usually an arrangement between the patient doctor and the treating doctor that fees should be paid. Where presents were given by the patient doctor they were usually commensurate with the services rendered.

In his judgment Mr. Justice Haugh said that prima facie where a doctor attended a doctor patient there was a contract that no charge should be made, and he had to be satisfied that Dr. Bradlaw knew that every time he paid a visit to Dr. Robinson he would be paying a fee about which there would be no legal dispute. It was unlikely that a doctor who had an express contract to pay another doctor two guineas a visit would give him presents or put his car at his disposal, as Dr. Bradlaw had. There was no cheque or letter from Dr. Bradlaw to support Dr. Robinson's case of an agreement to pay, and he was not satisfied that there had been such an agreement. He accordingly dismissed the action with costs.

Universities and Colleges

UNIVERSITY OF DURHAM

Professor F. H. Bentley, professor of surgery in the University of Durham, has left for the United States to give the Sommer Memorial Lectures in the University of Oregon, Portland, and to fulfil engagements in the departments of surgery in the University of Michigan, Ann Arbor, and the University of Illinois, Chicago.

UNIVERSITY OF LONDON

The title of Professor of Veterinary Anatomy in the University has been conferred on James McCunn, M.R.C.V.S., M.R.C.S., L.R.C.P., in respect of the post held by him at the Royal Veterinary College. The following have been appointed, or nominated for appointment or reappointment, as representatives of the University on the governing bodies indicated in parentheses: Sir Archibald Gray, Dr. C. F. Harris, and Dr. Andrew Topping (British Postgraduate Medical Federation); Mr. P. H. Mitchiner and Sir James Paterson Ross (Guy's Hospital Medical School); Dr. C. F. Harris (Committee of Management, Institute of Basic Medical Sciences); Mr. P. H. Mitchiner and Mr. M. F. Nicholls (Royal Dental Hospital of London School of Dental Surgery); Professor G. R. Cameron, F.R.S. (Royal Veterinary College); Mr. E. G. Slesinger (St. George's Hospital Medical School); Professor W. C. W. Nixon (St. Mary's Hospital Medical School); Mr. J. P. Hedley and Professor E. T. C. Spooner (St. Thomas's Hospital Medical School); Sir Archibald Gray and Dr. Andrew Topping (University College Hospital Medical School); Dr. A. J. W. Beard (King's College School, Wimbledon).

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *St. Thomas's Hospital Medical School:* Dr. J. E. M. Whitehead and Dr. J. L. Pinniger (Pathology). *St. Mary's Hospital Medical School:* Dr. R. R. Willcox (Venereal Diseases); Dr. J. F. Ackroyd (Medicine). *St. George's Hospital Medical School:* Dr. E. Levy (Pathology); Dr. J. R. Nassim (Medicine). *St. Bartholomew's Hospital Medical College:* Dr. D. A. MacDonald (Physiology). *Institute of Psychiatry:* Dr. T. McLardy (Pathology). *Postgraduate Medical School of London:* Dr. D. A. Mitchison, Dr. J. C. White, Dr. W. Hayes, and Dr. B. Lennox (Pathology). *Institute of Obstetrics and Gynaecology:* Mr. J. D. Murdoch and Mr. C. D. Read (Obstetrics and Gynaecology); Dr. J. Murray (Pathology). *Middlesex Hospital Medical School:* Dr. E. Neil (Physiology). *London Hospital Medical College:* Dr. A. d'A. Bellairs (Anatomy); Dr. G. W. Boden (Radiology); Dr. A. I.-P. Brown (Anaesthetics). *King's College Hospital Medical School:* Mr. W. P. Cleland (Surgery). *University College Hospital Medical School:* Mr. C. S. Hallpike (Oto-rhino-laryngology). *Royal Free Hospital School of Medicine:* Mr. H. E. Hobbs (Ophthalmology).

The October examination for Part I of the Academic Postgraduate Diploma in Psychological Medicine will begin on the fourth Monday in October, and the closing date for the receipt of entries is October 1. The April examination for Part II of the diploma will begin on the fourth Thursday in April, and the closing date for the receipt of entries is April 1.

UNIVERSITY OF BIRMINGHAM

Professor E. D. Churchill, professor of surgery in the University of Harvard and chief of the general surgical services, Massachusetts General Hospital, Boston, has accepted the invitation of the department of surgery of the University of Birmingham and the board of governors of the United Birmingham Teaching Hospitals to spend next month at the Queen Elizabeth Hospital as visiting professor. The University has conferred upon him the title of "Honorary Professor of Surgery." Professor Churchill is well known to British surgeons, and is an Honorary Fellow of the Royal College of Surgeons of England.

SOCIETY OF APOTHECARIES OF LONDON

At a meeting of the Court of Assistants held on August 21, with Dr. Frank D. Howitt in the chair, Dr. G. Roche Lynch was elected Master of the Society for the ensuing year: Sir Wilson Jameson and Brigadier E. M. Townsend were elected Wardens; and Dr. R. R. Trail was elected to a seat on the Court of Assistants, *vice* the late Dr. C. R. Box.

A portrait of Mr. Duncan C. L. Fitzwilliams, Immediate Past Master, by Maurice Codner, was accepted with gratitude. The resignation of Dr. Archibald Gilpin as Archivist to the Society was received with regret.

The following candidates were granted the diploma of L.M.S.S.A. upon examination: J. S. Green, M. H. Norman, G. H. Fisch, M. K. Panikkar, C. H. Wilkinson, J. C. Munro, J. P. Hewson, D. B. Evans, S. L. Soni, A. C. D. Abdool Raman, K. M. Dempsey, C. S. Osen, K. F. Thompson.

The Diploma in Industrial Health was awarded, by examination, to the following successful candidates: K. M. Basu, M. George, U. S. Gill, F. C. Myatt, R. H. Standbridge.

The Services

Surgeon Captain G. McCoull, O.B.E., V.R.D., R.N.V.R., has been appointed an Honorary Physician to the King, in succession to Surgeon Captain G. F. Abercrombie, V.R.D., R.N.V.R.

Surgeon Captain T. N. D'Arcy, C.B.E., R.N., has been appointed an Honorary Surgeon to the King.

Surgeon Commander M. J. L. Stening, R.A.N.R., has been awarded the Royal Naval Reserve decoration.

Surgeon Lieutenant-Commanders J. F. Foulkes, P. C. Barkla, and C. W. Levitt, R.N.V.R., has been awarded the R.N.V.R. decoration.

Brigadier J. C. Collins, C.B.E., late R.A.M.C., has been appointed a Deputy Director, Medical Services, and has been granted the temporary rank of Major-General.

A *Supplement* to the *London Gazette* has announced the following awards:

Four Clasps to the Territorial Efficiency Decoration.—Major H. Shield, M.C., T.D., R.A.M.C.

Three Clasps to the Territorial Efficiency Decoration.—Lieutenant-Colonel R. J. W. A. Cushing, T.D., R.A.M.C., retired.

First Clasp to the Territorial Efficiency Decoration.—Major (Honorary Lieutenant-Colonel) J. L. Orr, T.D., and Majors C. H. Johnson, T.D., W. F. de C. Veale, T.D., and A. Young, T.D., R.A.M.C.

Territorial Efficiency Decoration and First Clasp.—Major (Acting Colonel) A. G. Fleming, O.B.E., and Majors F. J. Fowler and J. E. Morrish, R.A.M.C.

Territorial Efficiency Decoration.—Major (Honorary Lieutenant-Colonel) W. R. P. Templeton, Captains (Honorary Majors) G. A. Hodgson, M.B.E., and A. C. McLaren, and Captain O. H. Belam, R.A.M.C.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending August 25 (No. 34).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland. (*e*) Eire. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending August 25					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	23	2	8		—	41	3	21	2	2	706	285	41
Deaths	—	—	—	—	—	—	—	—	—	—			
Dysentery	174	43	54	4		137	7	86		—	299	91	52
Deaths		—		—			—			—			
Encephalitis, acute	5	2	1	—		3	2	—		—	3	2	—
Deaths		—			—		—		—				
Erysipelas			17	1	5			20	4	4			
Food-poisoning	128	17		2		263	8		—				
Infective enteritis or diarrhoea under 2 years				9	79				8	23			
Deaths	7		1	1	—	11		3	—	2			
Measles*	2,352	51	62	106	64	4,277	316	79	26	64	4,277	2,140	987
Deaths		—	—	—	—			—	—	—			
Meningococcal infection	31	2	9	1	3	18	3	16	1		66	39	18
Deaths		—	—				—	—					
Ophthalmia neonatorum	40	1	4	—	1	34	2	6	—		130	74	34
Pneumonia, influenzal	181	12	1	2		177	10	—	2	2	353	299	177
Deaths (from influenza)†	2	—	—	—	—	1	1	—	—	1			
Pneumonia, primary			87					98					
Deaths	117	13		8	1	121	24		7	2			
Poliomyelitis, acute:													
Paralytic	60	3	} 17	} 5	} 2	} 589	} 42	} 86	} 18	} 5	} 676	} 34	} 15
Non-paralytic	56	1											
Deaths§	2	—			—	40	2			—			
Puerperal fever			7		1		—	6					
Puerperal pyrexia‖	240	32	1	1	1	85	10	7	—	1	168	126	85
Scarlet fever	436	29	120	5	27	635	50	137	37	27	1,894	812	489
Deaths		—	—	—	—			—	—	—			
Smallpox	—	—	—	—		—	—	—	—				
Deaths				—					—				
(1) Tuberculosis, respiratory			140	21				129	48				
(2) Tuberculosis, non-respiratory			22	5				37	8				
(1) Deaths	} 133	{ 13	12	3	9	} 132	{ 15	11	5	4			
(2) Deaths		5	3	1	3		2	3	—	—			
Typhoid fever	6	—	1	—	1	11	3	3	1	—			
Deaths¶	—	—	—	—		—	—	—	—				
Paratyphoid fever	46	4	1 (B)	9		10	1	3 (B)	—		102	29	21
Whooping-cough	2,948	134	307	45	132	3,725	354	238	31	80	3,725	1,818	1,152
Deaths	1	—	—	—	—	6	2	—	—	—			
Deaths (0–1 year)	208	33	29	7	10	165	24	29	3	13	335	297	165
Deaths (excluding stillbirths)	3,992	632	496	96	136	3,968	615	484	99	134	4,054	3,780	3,537
Annual death rate (per 1,000 persons living)			10·2					9·7					
Live births	6,571	1,119	858	195	419	6,681	1,090	844	200	433	8,394	6,684	5,909
Annual rate per 1,000 persons living			17·6					17·0					
Stillbirths	170	26	20			180	22	24			242	207	181
Rate per 1,000 total births (including stillborn)			23					28					

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London, and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

Vital Statistics

Poliomyelitis

Poliomyelitis notifications in the week ending September 1 were as follows (figures for the previous week in parentheses): paralytic 35 (60), non-paralytic 54 (56); total 89 (116). Up to and including the week ending September 1 the overall notification rate for England and Wales was 4.23 per 100,000. Although the proportion of non-paralytic cases tends to fall compared with the previous weeks it was still 60% for the week under review, which is higher than the normal.

Infectious Diseases

The chief fluctuations in the trends of infectious diseases in England and Wales during the week ending August 25 were falls in the number of notifications of measles 900, whooping-cough 211, and acute pneumonia 52.

A fall in the incidence of measles was recorded for the thirteenth consecutive week; the largest declines during the week were Durham 94 and Yorkshire West Riding 63. After reaching the highest level ever recorded during the eleventh week of this year, when 31,857 cases were notified, the notifications of measles are now a little below the usual seasonal level. The fall in the incidence of whooping-cough was mainly contributed by the northern counties and Wales, the largest decline being 71 in Lancashire. The notifications of diphtheria were 8 fewer than in the preceding week. The largest returns during the week were Lancashire 6, Staffordshire 4, Yorkshire West Riding 4, and these counties contributed over half the total cases in the country. The incidence of scarlet fever has been at a constant level during the past three weeks, and only small variations were reported in the local returns.

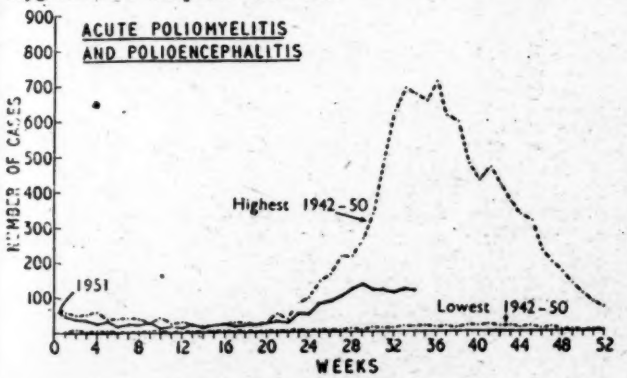
The notifications of paratyphoid fever were six fewer than in the preceding week. A further 14 cases were notified from the outbreak in Birmingham C.B.

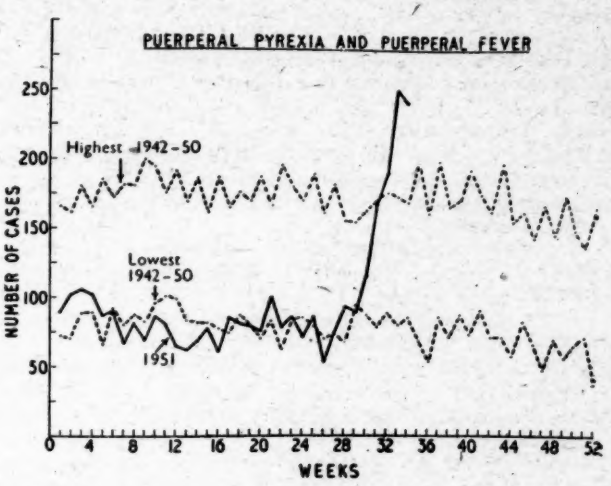
The notifications of acute poliomyelitis were 4 fewer than in the previous week, although the paralytic cases were 3 more. The incidence of this disease has remained almost constant during the past five weeks. The largest returns during the week were Lancashire 17 (Liverpool C.B. 6), Yorkshire West Riding 15, and Kent 7.

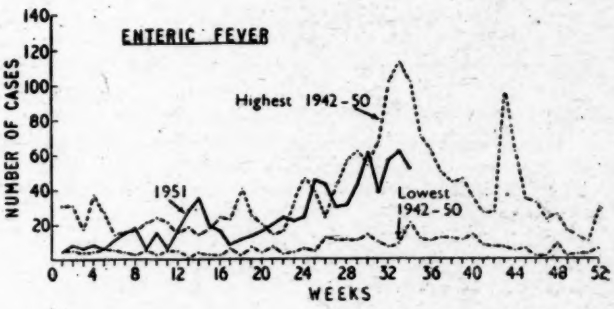
An increase of 21 was recorded in the number of notifications of dysentery. The rise was mainly due to an outbreak involving 31 persons in Surrey, Woking U.D. The other large returns of dysentery were 43 cases in London, distributed among 17 boroughs, and 14 in Yorkshire West Riding.

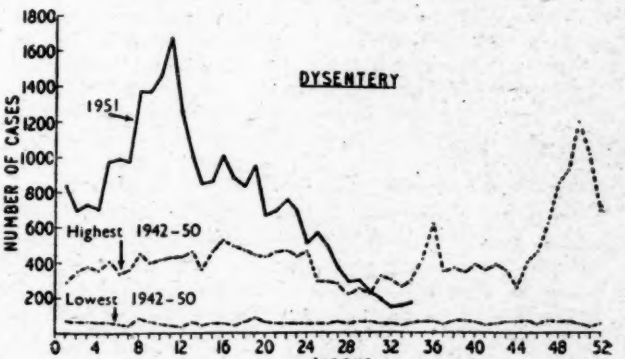
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus - - - - - - -, the figures for 1951 thus ————. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending September 1

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 461, whooping-cough 2,727, diphtheria 35, measles 1,876, acute pneumonia 217, acute poliomyelitis 89, dysentery 152, paratyphoid fever 37, and typhoid fever 2.

Unusually Low Infant Mortality

The infant mortality rate in Hammersmith M.B. in 1950 was 17 per 1,000 live births, which is a record low figure for the borough, and compares with 28 for the previous year. The figure of 17 is derived from 34 infant deaths out of 1,988 live births. Dr. F. M. Day, medical officer of health, gives this information in his *Annual Report* for 1950. In the same year the infant mortality rate for London was 26 and for England and Wales 29.

Public Health in Eire

The infant mortality rate in Eire in 1949 was 53 per 1,000 births, as compared with 50 for the preceding year (*Report of the Department of Health for Eire*, 1949–50). The increase over the rate for the previous year was due mainly to deaths from diarrhoea and enteritis. (In 1949 the infant mortality rate in England and Wales was 32, in Scotland 41,

and in Northern Ireland 45.) The birth rate was 21.5 per 1,000 estimated population. (In England and Wales it was 16.7, in Scotland 18.5, and in Northern Ireland 21.4.)

An unusual feature of the population in Eire is the high proportion of people who never marry. In 1946, the most recent year for which figures are available, the percentages of unmarried men and women over the age of 25 were as follows: in rural areas 46.6% of the men and 29.5% of the women, and in urban areas 33.7% of the men and 34.8% of the women.

As in the United Kingdom, there has been a great decrease in the incidence of diphtheria as the result of immunization. In 1945 there were 4,177 cases, with 236 deaths, while in 1949 there were 174 cases, with 10 deaths. But, as in England and Wales, the fatality rate remained much the same. In 1945 there were 5.6 deaths per 100 cases and in 1949 there were 5.7. These figures are slightly higher than those for England and Wales, where in 1949 the fatality rate was 4.4 deaths per 100 cases.

Medical News

Congress of Anaesthetists

Among the social events of the twenty-sixth annual congress of anaesthetists was a reception in the Great Hall of B.M.A. House by the Acting President, Sir Henry Cohen, on Monday, September 3. On September 4 there was a reception and dinner in the Grand Hall of Lincoln's Inn, under the presidency of Dr. I. W. Magill. At the dinner the health of the congress was proposed by the Dowager Marchioness of Reading, and the president responded. The health of the guests was proposed by Dr. V. F. Hall, and responses were made by Dr. Harold R. Griffith, of Canada, Dr. Torsten Gordh, of Sweden, and Dr. Ralph M. Tovell, of the U.S.A. On the following evening delegates to the congress attended a reception at the Royal College of Physicians, where they were received by Dr. W. Russell Brain and the Censors.

Outbreak of Ergotism

Over 200 inhabitants of the village of Pont St. Esprit (Gard), near Nîmes in the south of France, have recently suffered from ergot poisoning through eating affected bread. Below is a general view of the village, provided by the courtesy of Agence Intercontinentale, Paris.

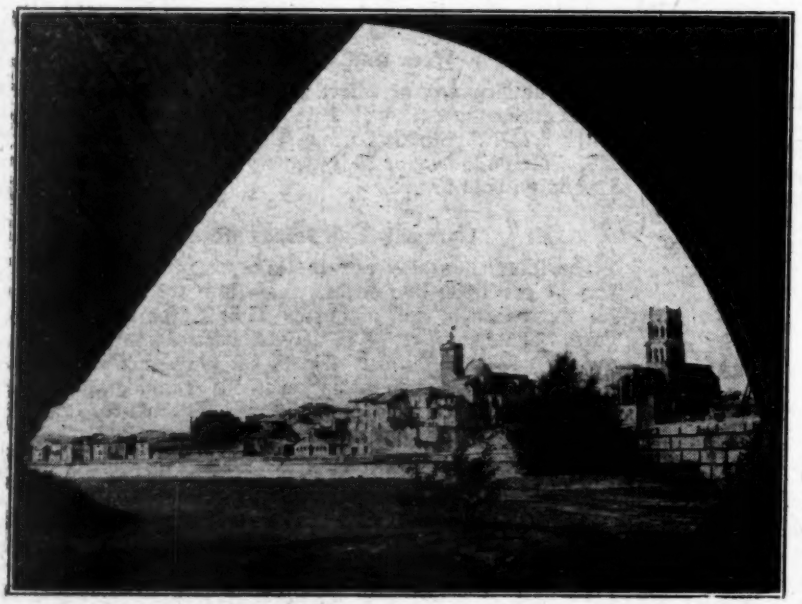


Photo by Agence Intercontinentale, Paris

Courses in Individual (Adlerian) Psychology

Dr. E. Weissmann writes: To complete the list of training facilities in psychiatry, psychotherapy, and medical psychology as published under "Courses in Psychiatry" (August 25, p. 487) it might be of interest to the medical profession—as a parallel to the Institute of Psycho-Analysis, which trains in psycho-analytic (Freudian) theory and technique—to know of the Institute of Individual Psychology (9, Fellows Road, London, N.W.3) for the training in Adlerian theory and technique. This Institute, under the auspices of the Alfred Adler Medical Society, is to start a part-time training lasting two to three years and including an Adlerian personal and training analysis, lectures and seminars, and clinical work under supervision in the near future. The introductory lecture course, covering the first term of three months, which can be taken as a separate course also, should begin in October.

Emergency Bed Service: Applications and Admissions

During the seven days ending September 10 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 665, of which 93.38% were admitted. This information will in future be published weekly in these columns. The applications include those from general practitioners and those from hospitals wanting to transfer patients from their casualty or out-patient departments. The gap between the number of applications and the number admitted is not composed entirely of cases that fail to be admitted. Some are cases withdrawn by the doctor or hospital while the E.B.S. is still working on the case, and some cases are of patients who refuse to go to hospital when a bed has been found or who die before admission.

COMING EVENTS

William Meredith Fletcher Shaw Memorial Lecture

Sir Eardley Holland will deliver the William Meredith Fletcher Shaw Memorial Lecture on "The Princess Charlotte of Wales: A Triple Obstetric Tragedy," before the Royal College of Obstetricians and Gynaecologists (58, Queen Anne Street, London, W.) on Friday, September 28, at 2.30 p.m. Admission is by ticket only, obtainable from the secretary of the College. A small collection of pictures, china, manuscripts, and other relics of Princess Charlotte will be on view in the Fellows' writing-room at the College from September 26 to October 6, 1951, inclusive, from 10 a.m. to 5 p.m. (Saturdays, 10 a.m. to 12 noon).

John Shields Fairbairn Memorial Lecture

The John Shields Fairbairn Memorial Lecture will be delivered by Dr. Nicholson J. Eastman, of Johns Hopkins Hospital, Baltimore, U.S.A., before the Royal College of Obstetricians and Gynaecologists (58, Queen Anne Street, London, W.) on Thursday, October 11, 1951, at 5 p.m. His subject is "The Causes and Management of Premature Birth." Admission is by ticket only, obtainable from the secretary of the College.

Medicine in Russia

Dr. Horace Joules, Dr. Ian Gilliland, and Dr. Mary Barber, who visited the U.S.S.R. this summer, will speak on their impressions of the Soviet medical services to a medical audience on Thursday, September 27, at 8 p.m., at the Society for Cultural Relations with the U.S.S.R., 14, Kensington Square, London, W.8. Medical guests are welcomed.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Wednesday

HEBERDEN SOCIETY.—At B.M.A. House, Tavistock Square, London, W.C., September 19, 5 p.m., *"The Adrenal Cortex and Rheumatoid Arthritis,"* Heberden Oration by Professor E. C. Kendall (Mayo Clinic).

LONDON COUNTY MEDICAL SOCIETY.—At Lambeth Hospital, Brook Drive, S.E., September 19, 3 p.m. Clinical meeting.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, London, W.—September 19, 3 p.m., *"Influenza Virus Research and its Biological Implications,"* Bengué Memorial Lecture by Professor Wilson Smith, F.R.S.

Saturday

BIOCHEMICAL SOCIETY.—At Rowett Research Institute, Bucksburn, Aberdeenshire, September 22, 11 a.m. Scientific papers.

APPOINTMENTS

CORMAC, C. D., B.M., B.Ch., D.P.H., Deputy County Medical Officer of Health and Deputy School Medical Officer, County of Bucks.

CRAWSHAW, DONALD GEORGE, M.B., Ch.B., D.P.H., D.C.H., Medical Officer of Health, Borough of Crewe, Divisional Medical Officer, Cheshire County Council.

CROWLEY, MATTHEW, M.B., B.Ch., D.P.H., Medical Officer of Health, Fareham, and Assistant County Medical Officer, Hampshire.

GUILD, A. A., M.B., Ch.B., M.R.C.P., Consultant Physician and Physician Superintendent, Lambeth Hospital, London, S.E.

JONES, D. M. MARTYN, M.B., Ch.B., D.P.H., Medical Officer of Health, Isle of Man.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—*Consultant Ophthalmologist, South Somerset Clinical Area,* A. E. Wilson, M.R.C.S., L.R.C.P., D.O.M.S. *Senior Surgical Registrar, Bristol Clinical Area,* P. C. Watson, M.B., B.S., F.R.C.S. *Senior Registrar in Obstetrics and Gynaecology, South Somerset Clinical Area,* Helen M. Russell, M.B., B.Chir., D.Obst.R.C.O.G., M.R.C.O.G. *Consultant Thoracic Surgeon, Bristol Clinical Area,* D. Mearns Milne, M.B., Ch.B., F.R.C.S.Ed. *Consultant Radiologist, Bristol Clinical Area,* K. H. Gaskell, M.R.C.S., L.R.C.P., D.M.R.D. *Psychiatric Registrars to South-west Region,* Brian Edgar, M.B., B.Ch., Anne French, M.B., Ch.B., and Merton Sandler, M.B., Ch.B. *Consultant Surgeon, Bristol Clinical Area,* T. J. Butler, M.B., Ch.B., F.R.C.S. *Anaesthetic Registrar to Frenchay Hospital, Bristol,* Aileen K. Adams, M.B., Ch.B., D.A. *Assistant Anaesthetist, Bristol Clinical Area,* Evelyn M. Lafferty, L.R.C.P.&S.Ed., D.A. *Assistant Anaesthetist, West Cornwall Clinical Area,* Jean Dutton, B.M., B.Ch., D.A. *Assistant Anaesthetist, Bath Clinical Area,* W. J. Lewis, M.R.C.S., L.R.C.P., D.A. *Anaesthetic Registrar, Frenchay Hospital, Bristol,* J. K. Trotter, M.R.C.S., L.R.C.P. *Senior Hospital Medical Officer, Roundway Hospital, Devizes,* R. H. Armin, M.B., B.Chir., D.P.M. *Consultant Paediatrician, Bath Clinical Area,* H. R. E. Wallis, M.D., M.R.C.P., D.C.H. *Consultant Pathologist, Bristol Clinical Area,* N. J. Brown, M.B., Ch.B., M.R.C.P. *Consultant Orthopaedic Surgeon, South Somerset,* A. E. Jowett, M.B., Ch.B., F.R.C.S.Ed. *Consultant Pathologist, Exeter Clinical Area (North Devon),* R. B. H. Tierney, M.D. *Consultant Paediatrician, Plymouth Clinical Area,* H. R. Jolly, M.D., M.R.C.P., D.C.H. *Consultant Chest Physician, West Cornwall,* B. A. Gwynne Jenkins, M.D., M.R.C.P. *Consultant Anaesthetist, Bristol Clinical Area,* Pamela Westhead, M.B., Ch.B., D.A.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Oddie.—On September 7, 1951, at The Limes, Bourn, Cambridge, to Romola, wife of J. A. Oddie, M.B., B.S., a son—Hugh Edward Toby.

DEATHS

Archibald.—On September 2, 1951, Thomas Dickson Archibald, M.D., of 90, Park Road, Toronto, Canada, aged 74.

Bain.—On August 28, 1951, at 12, Darnaway Street, Edinburgh, John Haldane Bain, L.R.C.P.&S.Ed., L.R.F.P.S., L.D.S.

Black'ev.—On August 31, 1951, William John Blackley, M.B., Ch.B., of Killermont, Hyndford Road, Lanark.

Bumsted.—On August 30, 1951, at "Elmfield," 84, Leigham Court Road, Streatham, London, S.W., Henry James Bumsted, M.B., B.Ch.

Davidson.—On August 30, 1951, at a nursing-home, Glasgow, Norman Grenville Walshe Davidson, O.B.E., F.R.C.S.Ed., of 6, Lynedoch Place, Glasgow.

Debenham.—On September 8, 1951, Horace Allan Debenham, M.R.C.S., L.R.C.P., of Warden, Whiteleaf, Princes Risborough, Bucks, formerly of Presteigne, Radnorshire, aged 87.

Edge.—On August 25, 1951, at Cornerways, The Park, Cheltenham, Arthur James Broughton Edge, M.B., aged 87.

Ellis.—On August 26, 1951, at Carshalton, Surrey, Mary Ellis (formerly Gardner), M.B., Ch.B., aged 79.

Johnston.—On August 29, 1951, at a nursing home, Taunton, William Johnston, M.D., of Corfe, near Taunton, Somerset, aged 65.

Leslie.—On August 28, 1951, at Collards, Haslemere, Surrey, William Murray Leslie, M.D., F.R.C.S.Ed., aged 92.

MacInnes.—On August 30, 1951, at Stoer, Sutherland, Ian Lamont MacInnes, M.B., Ch.B.

Ninnis.—On September 6, 1951, Roger Paul Ninnis, M.B., B.S., Surgeon Captain, R.N., retired, aged 60.

Penhale.—On September 1, 1951, at Pendaw, Great Barr, Birmingham, William Percivall Penhale, M.R.C.S., L.R.C.P., aged 60.

Sephton.—On September 1, 1951, at 17, Woodland Avenue, Bournemouth, Robert Poole Sephton, M.R.C.S., L.R.C.P., husband of Nancy Sephton, M.B., Ch.B.

Slaughter.—On August 25, 1951, Ernest Augustus Slaughter, M.D., of "The Grendons," Teignmouth, Devon, aged 87.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Preservation of a Corpse

Q.—*I should be glad to have information about the cause of delayed putrefaction. The body of a man was found in good condition after four days, without discoloration of any of the organs or any smell. The atmosphere was dry and the average temperature 70° F. (21° C.). Could this be due to a process such as mummification? If so, what conditions could produce it, and what would be the findings on the fourth day? Is there any known poison which could cause sudden death and then delay putrefaction?*

A.—The only common reasons for striking preservation of the body are intense cold or dry heat, and a continuous dry atmosphere at 70° F. could very well account for delay—even indefinite delay—in putrefaction. Mummification would ultimately develop, but it would be hardly appreciable in as little as four days, except perhaps as some crinkling in the finger pads. Mummification requires: (*a*) relative scarcity (or complete absence) of the putrefying clostridial organisms normally present in the bowel—this condition is commonly satisfied in the newborn infant, whose bowel is still sterile; (*b*) dry heat, preferably moving currents of dry air; and (*c*) time. Weeks may elapse whilst the body almost imperceptibly becomes drier: moulds may grow on the skin and the larvae of insects may gain a hold on or worm their way into the tissues, but putrefaction does not develop, the body just drying. Of the preservative poisons, arsenic and antimony salts absorbed over a long period are the only really effective agents. Sudden death from any form of either of these should be obvious upon examination of the stomach and intestines, which would be highly irritated by the dose required to kill. Poisoning is therefore only a remote possibility.

Mixed Injection of A.T.S. and Penicillin

Q.—*Is it possible to give a mixture of anti-tetanus serum and penicillin in the same syringe without adverse effect? It would be very useful to do so in young children in out-patient departments.*

A.—There is no reason why penicillin and tetanus antitoxin should not be mixed in the same syringe prior to injection. It has been objected that procaine penicillin should not be mixed with watery solutions, but the most up-to-date procaine penicillin is prepared now in an aqueous suspension, and in any case the substance is transferred to an aqueous medium as soon as it is injected into the tissues.

Medical Treatment of Cholecystitis

Q.—*What is the best medical treatment of chronic cholecystitis? No gallstones are visible either on the plain x-ray film or after cholecystography. The patient is a man of 40 who has had enteric fever and repeated attacks of malaria; he resides in Rhodesia.*

A.—The medical treatment of chronic cholecystitis resolves itself into an attempt to control any infection that may be present, to drain the bile passages as freely as possible, and to give dietetic advice designed to throw as little strain as possible on the process of digestion and absorption of fat.

It is unfortunate that the antibiotics at present in use are not particularly effective in combating chronic gall-bladder infection, but chloramphenicol in 0.5-g. doses, six-hourly, in courses of five to seven days, or penicillin, may be used with the first objective in mind. The second is best

attempted by taking regular doses of an efficient cholagogue, such as dehydrocholic acid, two or three times a day. This may have a mild laxative effect, but magnesium sulphate in the morning in addition is worth giving also. The diet should be kept low in fat and moderate in calorie value to combat any tendency to obesity. Cooked animal fats in particular should be avoided, as should all fried food. Foods of a high cholesterol content are best taken in small amounts. These include all glandular organs—such as liver, brains, kidneys—dairy products, cakes, muffins, and hot breads.

Symptomatically flatulence is often the most disturbing symptom, and for this olive oil—a neutral fat—can be given with impunity and is really valuable. The oil should be fresh, when it will be tasteless, and the dose should be ½ to 1 fl. oz. (14 to 28 ml.) before meals.

It has been assumed that in the case in question there is no evidence of persistence of the enteric infection.

Intestinal Myiasis

Q.—*What is the treatment of intestinal myiasis? I have a case now in a young negro with severe diarrhoea, intermittent vomiting, abdominal pain, and wasting over a period of several months, according to his history. His motions are teeming with maggots, which I think are Chrysomyia chloropyga. I am well isolated in the bush and have few facilities for laboratory tests, but so far have been unable to find any other abnormality to cause his symptoms and signs. The psychological distress in intestinal myiasis is considerable even when physical ill effects are not pronounced.*

A.—It seems incredible that flies could go on breeding within the intestinal canal over a period of several months, and consequently persistent intestinal myiasis must be due to ingestion of eggs or larvae, unless there is some simple explanation for the apparent infection, such as the deposition of eggs around the anus or in the faeces after they have been passed. It follows therefore that treatment depends upon the application of proper hygienic methods rather than the administration of any drugs.

Heredity of Congenital Dislocation of the Hip

Q.—*To what extent is congenital dislocation of the hip a hereditary condition? Is there an increased possibility of this condition occurring in the children of a woman who herself suffered from congenital dislocation of the left hip?*

A.—There is a definite hereditary element in this condition. It may well be that the genetic basis is a gene which is often not expressed, particularly of course in boys. The chance that this woman will have a similarly affected child is higher than for a normal woman, but it is not a big risk—not greater than, say, one in twenty or one in thirty.

Immunity to Tuberculosis after Lung Resection

Q.—*(1) Does a patient ever become tuberculin negative after a complete resection of a tuberculous lung lesion? (2) Is the general level of immunity likely to be altered at all? (3) Is continued exposure to known sources of infection at work, or in the home, likely to be a factor of any importance in causing late post-operative breakdowns?*

A.—No definite answer can be given to any of the three questions. (1) No observations have been published which would give an answer to the first.

(2) It is generally accepted that the partial specific resistance developed following a single tuberculous infection does not last a lifetime; but it probably does persist, even in the absence of fresh infection, for some considerable time after the healing of the infection which provoked its production, and it is probably reinforced by chance reinfections when these do not provoke disease. On this basis one can say that the general level of immunity is not likely to be altered for some time after resection of a tuberculous lung lesion, even if that resection has removed the sole focus of infection in the body.

(3) In tuberculosis, resistance to fresh infection is probably never complete. A person whose lung lesion has been resected is not immune in any absolute sense, and some "late post-operative breakdowns" could be due to fresh disease set up by added infections. However, it would hardly ever be possible to say in any single case if such a breakdown was due to fresh infection or to spread of an active lesion left untouched by the resection.

Androgen Therapy and the Risk of Recurrence of a Seminoma

Q.—*Two years ago a man of 36 had a bilateral orchidectomy and x-ray therapy for a seminoma of an undescended testis. Would a testosterone implant increase the chances of a recurrence?*

A.—There is no evidence to suggest that the administration of androgens would lead to metastatic recurrence of a seminoma. No one has suggested that androgens are neoplastic agents. On the other hand, androgens would certainly relieve the symptoms—hot flushes, impotence, etc.—of bilateral orchidectomy.

Clarionets and Asthma

Q.—*Is the playing of a wind instrument (clarionet) contraindicated in a child who has occasional attacks of asthma?*

A.—There is no reason why a child with occasional attacks of asthma should not play a wind instrument. There is no evidence that this leads to emphysema. It is even possible that the expiratory effort might be helpful in overcoming the asthma.

Alum and Chlorine in the Water Supply

Q.—*The water supply in this town (South India) is treated with alum and chlorinated. Is ingestion of such water continuously over several years harmful?*

A.—Both alum and chlorine have been used for many years in the treatment of water throughout the world, and there is no record of any harm having been caused to consumers.

NOTES AND COMMENTS

Deck Legs.—Dr. J. E. JENKINS (Birmingham) writes: The cause and cure would appear to be much simpler than in the answer published on August 11, p. 372. Observation will show that "deck legs" are directly related to the wearing of rubber-soled shoes or gym shoes. Wearing leather-soled shoes will prevent the condition, or resumption of their wear will clear the condition in two or three days. During the war, on a troopship with between 2,000 and 3,000 troops aboard, we were overwhelmed with cases of "deck legs." An order that all ranks should wear leather-soled shoes again in place of the universally used rubber-soled gym shoes cleared the ship of all cases within a few days. On a later trip, limited wearing of rubber-soled gym shoes was allowed, and no cases of "deck feet" were encountered.

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